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AMERICAN JOURNAL
OF
OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON

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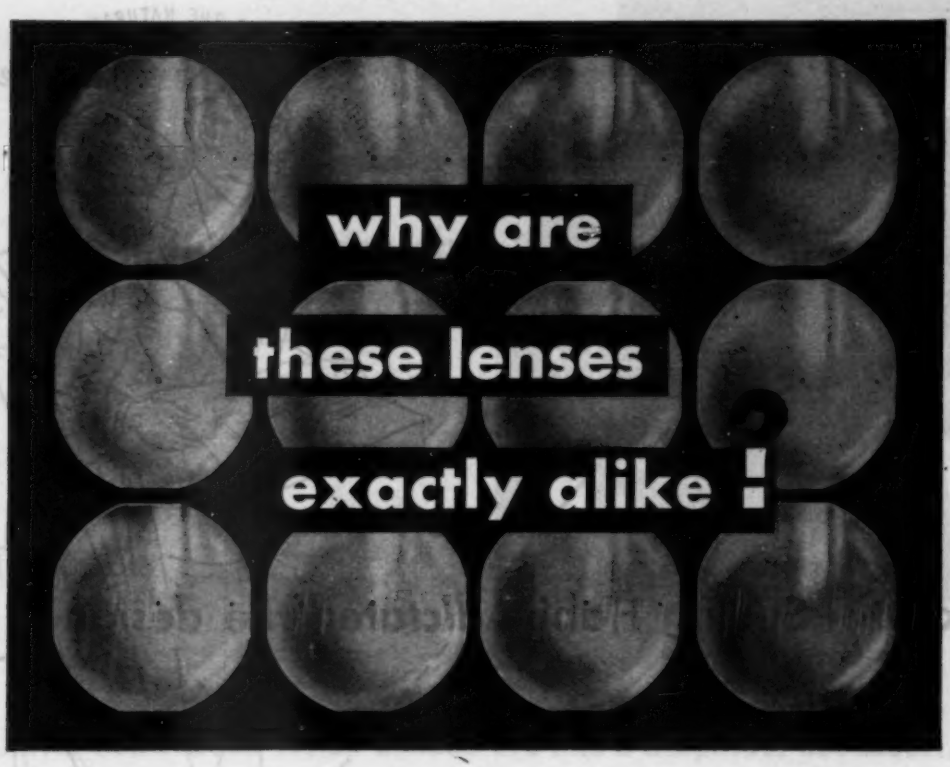

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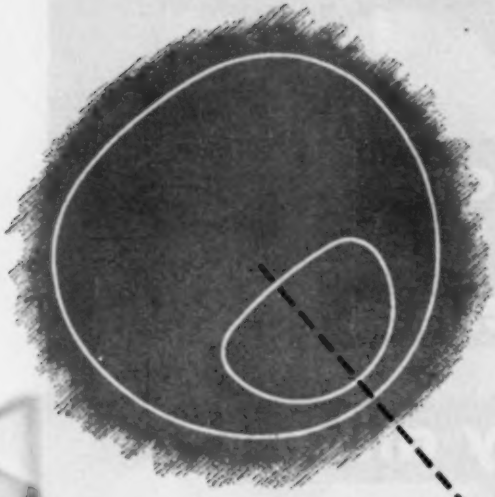

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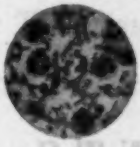
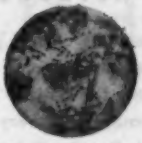


...in ocular infections



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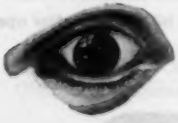

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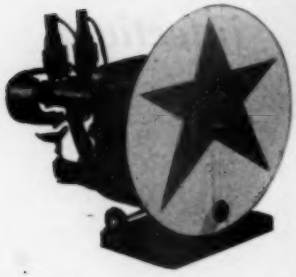

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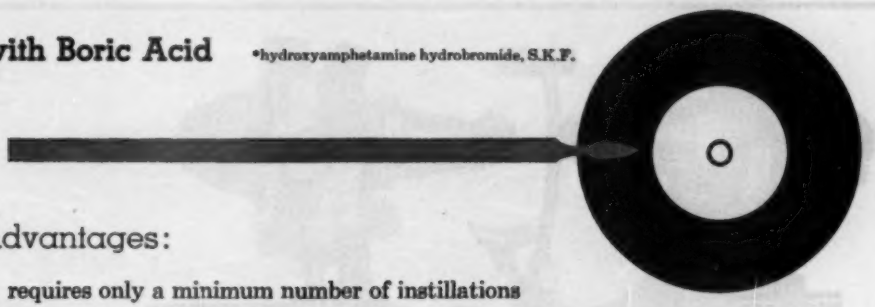

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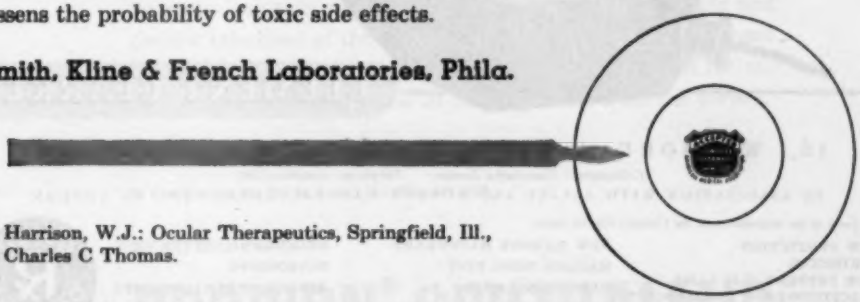

1. Harrison, W.J.: Ocular Therapeutics, Springfield, Ill., Charles C Thomas.

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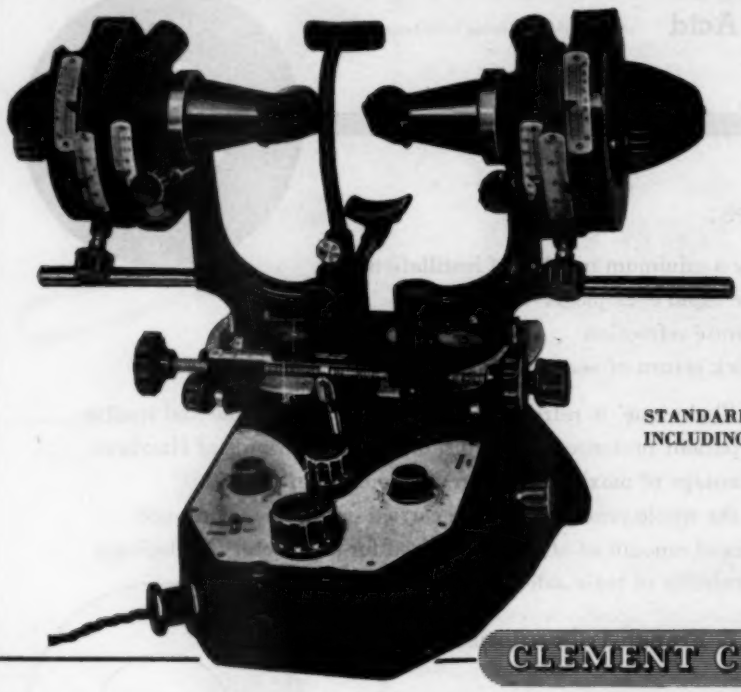

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1. Theodore, F. H.: J.A.M.A. *143*:226 (May 20) 1950.

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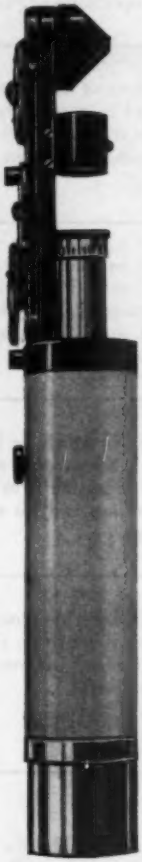

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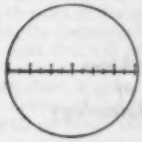
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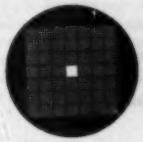
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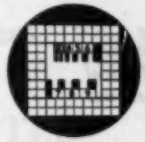
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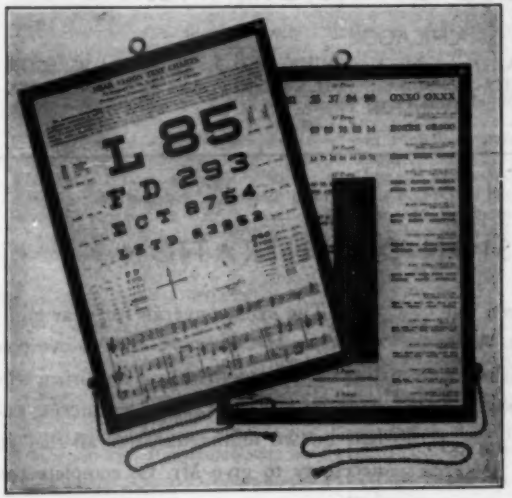

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"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

AMERICAN JOURNAL OF OPHTHALMOLOGY

SERIES 3 · VOLUME 34 · NUMBER 5 · PART I · MAY, 1951

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ABSTRACTS

Physiologic optics, refraction, color vision; Diagnosis and therapy; Ocular motility; Conjunctiva, cornea, sclera; Uvea, sympathetic disease, aqueous; Glaucoma and ocular tension; Crystalline lens; Retina and vitreous; Optic nerve and chiasm; Neuro-ophthalmology; Eyelids, lacrimal apparatus; Tumors; Injuries; Systemic disease and parasites; Congenital deformities, heredity; Hygiene, sociology, education, and history 779

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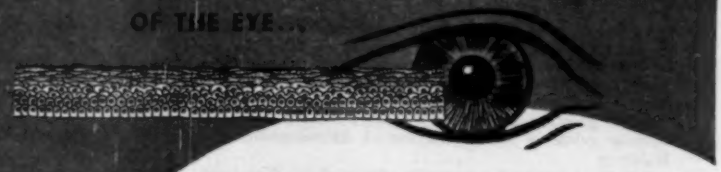

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FIG. 12 (BECKER AND POST). FUNDUS OF A CAT 10 DAYS FOLLOWING VENOUS OCCLUSION. NOTE THE DILATED TORTUOUS VEINS, THE FLAME-SHAPED HEMORRHAGES ALONG THE VEINS, THE EXUDATES OBSCURING THE TAPETUM, THE RELATIVELY NORMAL ARTERIES, AND PARTICULARLY THE SMALL ANEURYSMS ASSOCIATED WITH THE VENOUS END OF THE CAPILLARIES.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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RETINAL VEIN OCCLUSION*

CLINICAL AND EXPERIMENTAL OBSERVATIONS

BERNARD BECKER, M.D., AND LAWRENCE T. POST, JR., M.D.
Baltimore, Maryland

The recent work on the vascular pathology of diabetic retinopathy[1] indicates a striking similarity between this disease and two others: Eales's disease and central vein occlusion. An experimental investigation of certain phases of these diseases was therefore undertaken in the hope that some more concrete evidence of this similarity might be discovered.

Specifically, in view of the demonstration of aneurysms[2] in the retinal capillaries in diabetic retinopathy, it was thought likely that aneurysms of similar nature might be present in cases of central vein occlusion and Eales's disease. With this in mind, all cases of vein occlusion in the clinical and pathologic files of the Wilmer Institute were reviewed, and the possibility of producing central vein occlusion in the experimental animal was explored.

I. CLINICAL

In order to compare statistics, the literature on venous occlusion was reviewed, and from this review certain generalizations are in order.

Although, soon after the invention of the ophthalmoscope, central vein occlusion was illustrated in the ophthalmologic atlases, its essential nature was not described until the report of Michel[3] in 1878. He believed that the majority of such occlusions were caused by thrombosis, but he described one case in which no thrombus could be found and in which intimal proliferation seemed to play an important part.

There followed a series of papers by Coats[4] and Verhoeff[5] in which this controversy was intensified and never really satisfactorily resolved. Coats contended that most cases were due to thrombosis, while Verhoeff was equally sure that they were due to endothelial proliferation.

With the publication of several papers by Scheerer[6] in the early twenties, the enthusiasts for intimal proliferation seemed to be in the ascendency, but with the advent of anticoagulants, it became immediately apparent that the idea of thrombosis still had its large group of adherents. Suffice it to say that at present there is still no real agreement, and it is not our intention to enter into this debate.

This study, however, brought out several less frequently discussed points which appear worth emphasizing. In the files of the Wilmer Institute, there were over 150 diagnoses of vein occlusion, but because of incomplete records only 59 eyes in 57 patients were suitable for analysis. This material consisted of 15 branch occlusions and 44 central occlusions. The study was also limited by the fact that the diagnostic index of the Wilmer Institute is limited to patients admitted to the hospital; out-patient diagnoses are not indexed. Therefore, the cases of central vein occlusion included in this series are almost exclusively either of the patients

* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital. Presented at the ninth annual meeting of the Wilmer Residents Association, April, 1950.

with glaucoma, or of those admitted for diagnostic surveys.

Seven of the branch occlusions were in the superior temporal vein, five in the inferior temporal vein, and only one was an isolated nasal branch occlusion. This is in good agreement with the large series reported by Foster Moore,[7] Jensen,[8] Koyanagi,[9] and Allaire,[10] whose over-all statistics revealed 87 (65 percent) superior temporal, 40 (30 percent) inferior temporal, and only two isolated nasal occlusions.

Gradle,[11] Duke-Elder,[12] and others have been impressed with the frequency with which vein occlusion occurs in cases with preëxisting glaucoma. In 1913, Verhoeff[13] reviewed the pathology of 39 cases of glaucoma secondary to anterior segment disease and discovered that in all of these cases there was endovasculitis in either one or both of the central vessels; 83 percent of the central veins showed endophlebitis, and 33 percent of the cases showed either partial or complete obstruction of the central retinal vein.

In the various clinical reports there has been a similar high percentage of cases occurring in primary and more frequently in secondary glaucoma. In this series, in 10 of 44, or 23 percent, of the central vein occlusions and in one of the 15 branch occlusions, the occlusion was preceded by an elevated ocular tension.

A review of the literature suggests two distinct types of glaucoma occurring in eyes with vein occlusion; first, an acute, hemorrhagic glaucoma following a latent period, characterized by rubeosis iridis, high tension, and an extremely poor prognosis; and secondly, a less dramatic, more benign glaucoma, without rubeosis, nonhemorrhagic, without a characteristic latent period, and without acute onset.[14]

The cases in this series tend to bear out the apparent fact that the latter type is not secondary to the vein occlusion, but that either the glaucoma precedes and is responsible itself for the occlusion, or that glaucoma and occlusions tend to occur in eyes with similar vascular disturbances.

A nice illustration is afforded by two of the patients in this series who developed central vein occlusion superimposed on glaucoma simplex, and who later, after an appropriate latent period, had a sudden, additional increase in tension, developed rubeosis, pain, and eventually came to the inevitable loss of the eye.

The general prognosis in branch occlusion in all reported cases is a tendency to improvement over a period of years without the development of glaucoma. There are only two cases of hemorrhagic glaucoma secondary to branch occlusion reported in the literature. One of these is reported by Uhtoff[15] in which no details are given, and one by Jensen,[8] which from the history appears to have been in all probability a case of central vein occlusion. Apparently, therefore, hemorrhagic glaucoma does not occur secondary to a branch occlusion.

The prognosis in central vein occlusion is poor, with a tendency to steady deterioration of the eye. Ten to 20 percent of these patients develop hemorrhagic glaucoma, and these seem to have a particularly dismal outlook. In this series all eyes with true hemorrhagic glaucoma secondary to vein occlusion came eventually to enucleation.

II. Pathologic

In fundus pictures of "retinal apoplexy" in the early atlases, small aneurysmal dilations of the vessels are clearly depicted. Coats[16] mentioned "miliary angiomata" in his pathologic descriptions. Recently these lesions, which previously had been alluded to only indefinitely, were established on a firmer foundation when Loewenstein[17] published his description in 1945 of capillary aneurysms and demonstrated them by scarlet-red staining of flat preparations of the retina. We have recently become aware that work similar to ours on flat preparations of the retina is being carried out by Ballantyne[18] and his associates in

Fig. 1 (Becker and Post). Typical chains of saccular aneurysms on the venous side of the capillary circulation in central vein occlusion. Note the tremendously dilated aneurysms as compared with the size of the surrounding relatively normal capillaries.

Fig. 2 (Becker and Post). An isolated, thick-walled, saccular aneurysm in central vein occlusion. There are surrounding exudates and deformity of the capillary pattern, probably representing newly formed vessels.

Fig. 3-A (Becker and Post). Chain of aneurysms in a case of central vein occlusion.

Fig. 3-B (Becker and Post). High-power view of one of the aneurysms in Figure 3-A.

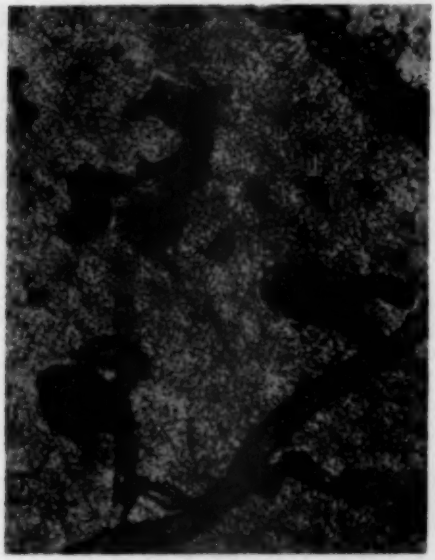

Fig. 4 (Becker and Post). Marked distortion of capillaries, with large, dense aneurysms and exudates in a case of central vein occlusion.

Fig. 5 (Becker and Post). Flat preparation from a case of diabetes with marked diabetic retinopathy in which many large, thick-walled aneurysms in clusters were found throughout the retina in all parts of the capillaries. The photograph represents one area in that retina in which there are chains of aneurysms as well as large, isolated aneurysms. This may represent a superimposed, small branch venous occlusion.

Glasgow, Scotland, with similar results.

Flat preparations of retinas, when stained for polysaccharides by the Hotchkiss method, reveal the intimate details of the vascular and in particular the capillary network.[1] Since this method has proved to be so profitable in the demonstration of the capillary aneurysms of diabetic retinopathy, it seemed reasonable to apply this technique

Fig. 6 (Becker and Post). Distortion of the vascular pattern with newly formed capillaries on the surface of the retina in a case of central vein occlusion.

to cases of Eales's disease and central vein occlusion.*

To date 39 cases of central vein occlusion

* Preliminary incubation of eyes at room temperature for 24 to 36 hours before fixation has proved most valuable in obtaining better differentiation of the capillaries, which survive the more rapid autolysis of the rods and cones.

selected from the files of the pathology laboratory of the Wilmer Institute have been studied, all patients with diabetes being excluded. This of necessity has limited the material to eyes which were enucleated for hemorrhagic glaucoma in patients in whom there was a definite history of central vein occlusion or actual observation of occlusion some weeks or months before.

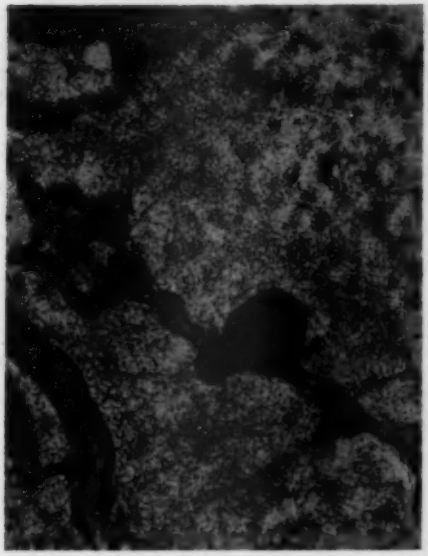

Fig. 7 (Becker and Post). Aneurysms with distortion and newly formed capillaries in central vein occlusion.

Six of the cases, however, were found as chance findings at routine autopsy with no history or evidence of glaucoma. In each of these 39 cases of central vein occlusion, capillary aneurysms were found. It is, of course, conceivable that some of these cases had undiagnosed diabetes, but the findings were consistent in all cases, and in many there were definite records of the absence of glycosuria and the presence of normal fasting blood sugars, and in several there were normal glucose tolerance curves.

The most consistent and typical type of deformity of the capillaries that was ob-

Fig. 8 (Becker and Post). Tremendous distortion of the capillaries, which are folded and twisted on themselves and in a plane anterior to that of the retina. Aneurysms are also present in this case of central vein occlusion.

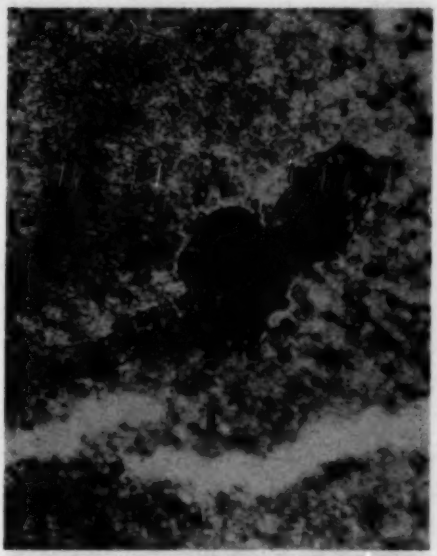

Fig. 9 (Becker and Post). A coiled capillary protruding forward into the vitreous which appears collapsed onto the surface of the retina in this preparation from a case of central vein occlusion.

Fig. 10-A (Becker and Post). An isolated aneurysm in a flat preparation of the retina from a case of Eales's disease. In this case there was considerable retinal edema, hemorrhages, and retinitis proliferans, and therefore, the preparation is not well differentiated.

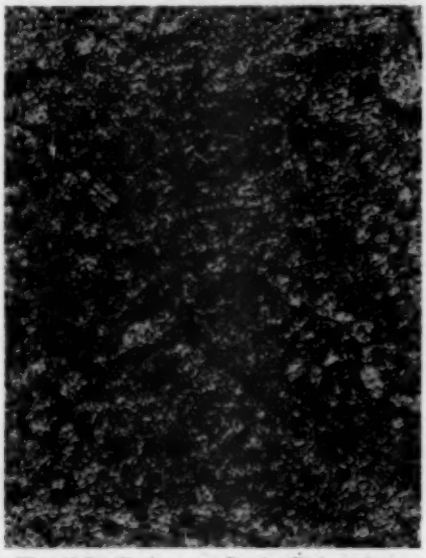

Fig. 10-B (Becker and Post). Chains of aneurysms in another area of the retina in the same case of Eales's disease as is shown in Figure 10-A.

served in these cases of central vein occlusion was chains of saccular aneurysms on the venous side of the capillary circulation (figs. 1 and 3). In some instances isolated, thick-walled, saccular aneurysms of a type quite similar to those found in diabetes were found, but they were invariably confined to the venous end of the capillary (figs. 2 and 5). Hemorrhages and exudates surrounded, and were closely associated with, the microaneurysms (figs. 2 and 4). Remarkable distortion of capillary architecture and newly-formed capillaries on the surface of the retina (retinitis proliferans) were found frequently (figs. 6, 7, 8, and 9).

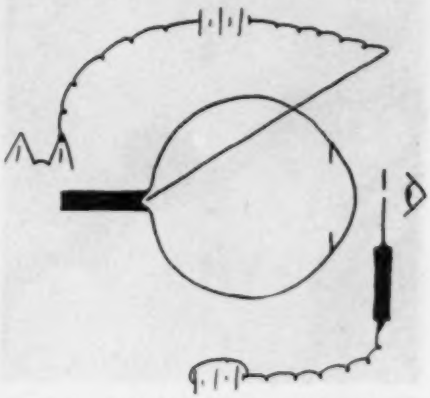

Fig. 11 (Becker and Post). Diagrammatic representation of method utilized to produce experimental venous occlusion.

In the one case of Eales's disease so far investigated, both isolated aneurysms and chains of aneurysms were found (fig. 10).

III. Experimental

Various forms of therapy and innumerable theories as to the pathogenesis of diabetic retinopathy, central vein occlusion, and Eales's disease have been proposed. It seemed possible, therefore, that considerable information on the pathogenesis and therapy of this group of diseases might be obtained if a method could be devised for producing

such lesions in animals. Attempts have been made to produce diabetic retinopathy in rabbits made diabetic with alloxan, but thus far without success. We wish to describe a technique for occluding retinal veins and to present preliminary observations and results.

Rabbits were first used, but because of their inadequate retinal circulation it was necessary to change to cats. A 120 micron "nichrome" wire was utilized that was insulated except at its tip, which was filed smooth. One end of the wire was attached to the diathermy machine and the other introduced into the eye at the pars plana of the ciliary body or in the peripheral retina, after preliminary cauterization and diathermy to the surrounding area of sclera. Under direct observation with an ophthalmoscope (fig. 11), the wire could be directed back through the vitreous until it was in the deep cup of the optic nerve.

In the normal cat fundus there are three

Fig. 13-A (Becker and Post). Organizing thrombi in central vein of cat's retina 10 days following experimental occlusion.

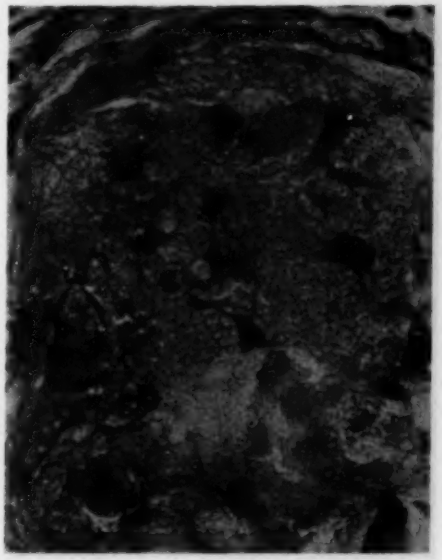

Fig. 13-B (Becker and Post). High-power view of thrombosed vessels in Figure 13-A. Note the fibroblasts growing into the thrombus.

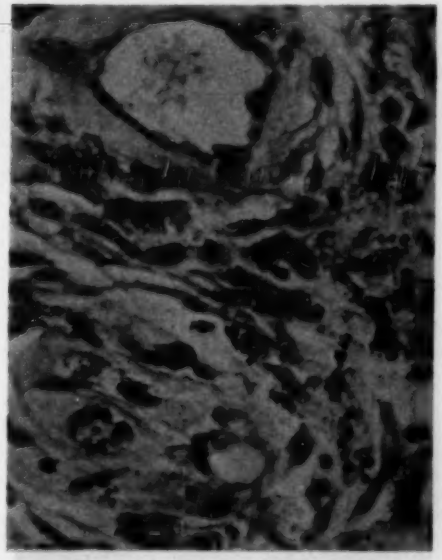

Fig. 14 (Becker and Post). Relatively normal artery with a thrombosed vein next to it near the disc in a cat's retina 10 days following experimental occlusion. Note the phagocytized blood pigment.

Fig. 15-A (Becker and Post). Thrombosed vessel with beginning recanalization in a cat's retina following venous occlusion.

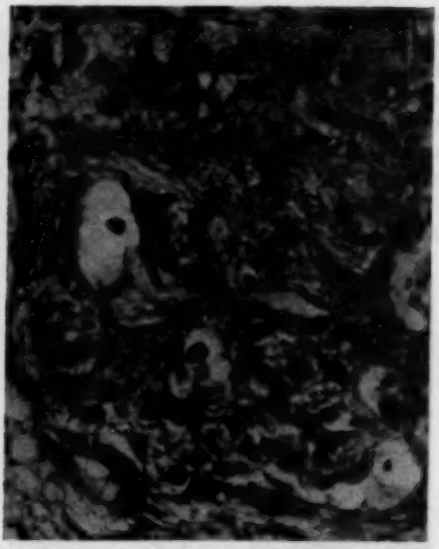

Fig. 15-B (Becker and Post). High-power view of Figure 15-A.

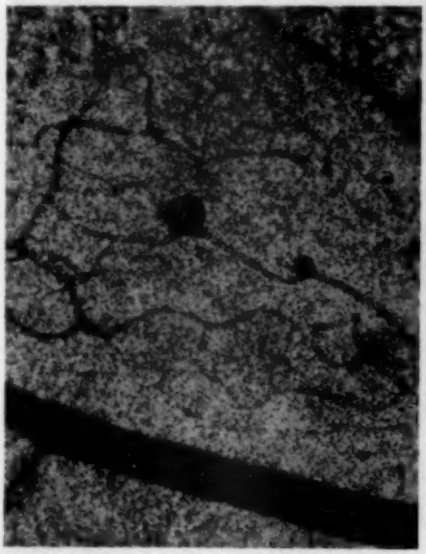

Fig. 16 (Becker and Post). Isolated, thick-walled aneurysm in a flat preparation of the retina of a cat three months following experimental occlusion.

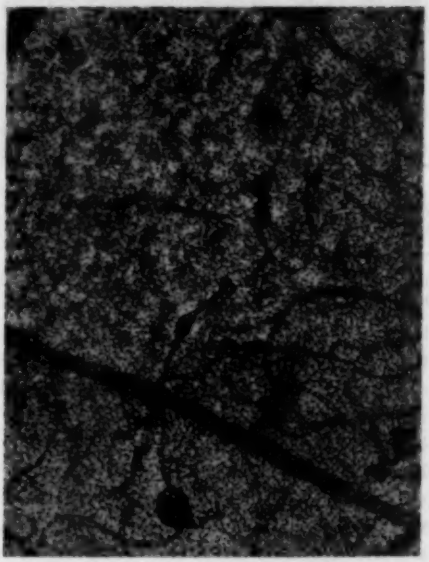

Fig. 17 (Becker and Post). Isolated aneurysms as well as chains of capillary aneurysms in the retina of a cat three months following experimental venous occlusion.

branches of the central retinal artery and vein (superior temporal, inferior temporal, and nasal) and seven to 10 smaller cilioretinal arterioles coming off the deeply cupped disc.[19]

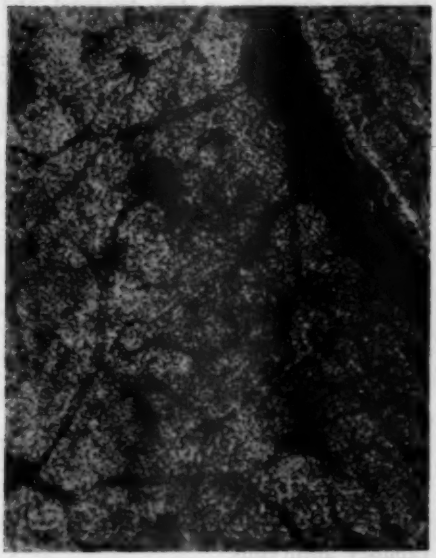

Fig. 18 (Becker and Post). Isolated, thick-walled aneurysm and distortion of capillary pattern in flat preparation of cat's retina after venous occlusion.

With the electrode in the cup but touching no vessels, a standard current was applied for 10 seconds. There was immediate liberation of gas bubbles in the vitreous as a result of the heat at the tip of the electrode, as well as constriction of arterioles and marked dilation of the veins.

In successful cases no hemorrhages or exudates were visible at the close of the procedure. Fifteen to 20 hours later, however, hemorrhages and exudates were noted beginning in the far periphery. These increased in number, and in two to three days the fundi showed relatively normal arteries, dilated, tortuous veins associated with exudates, and large, flame-shaped hemorrhages, retinal edema, capillary aneurysms, round hemorrhages, and occasional hemor-

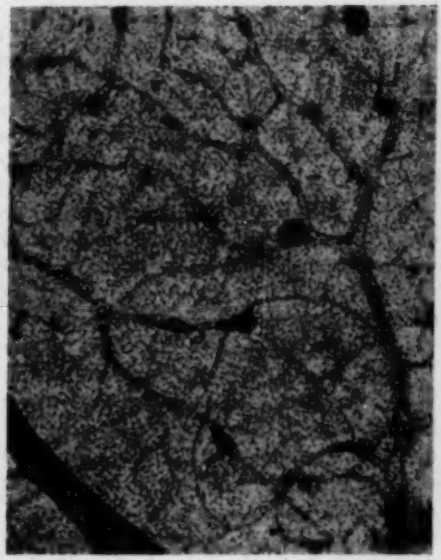

Fig. 19 (Becker and Post). Capillary aneurysms in cat's retina following experimental venous occlusion.

Fig. 20 (Becker and Post). Marked distortion of capillary pattern with giant aneurysm in flat preparation of cat's retina two months after experimental venous occlusion.

rhages into the vitreous. This picture closely simulated clinical vein occlusion.

Attempts to photograph cat fundi met with little success. We are indebted to Mrs. Burgess for her excellent painting of the fundus of a cat 10 days following operation (fig. 12).

Serial sections of such eyes revealed hemorrhages, exudates, and venous thrombi which became organized and recanalized. In spite of intensive search no abnormalities in the choroid or in the disc itself could be found (figs. 13, 14, and 15).

In order to determine if these induced venous occlusions would compare pathologically with those occurring in humans, the basement membrane stain for flat preparations was modified to permit its use on animal retinas.* By means of this technique, isolated capillary aneurysms, chains of aneurysms at the venous end of capillaries, distortion of capillary architecture, and newly formed vessels could be clearly demonstrated (figs. 16, 17, 18, 19, and 20).

While no conclusions can be drawn from these preliminary observations, they appear to indicate some similarity in the vascular pathology of diabetic retinopathy and central vein occlusion.

Summary

1. The literature and the cases of central vein occlusion in the Wilmer Ophthalmological Institute are reviewed.

2. Branch occlusions in almost all cases are seen clinically in the temporal and especially superior temporal veins and are apparently never followed by hemorrhagic glaucoma.

3. Central vein occlusion is more common in patients with chronic glaucoma.

4. Hemorrhagic glaucoma secondary to central vein occlusion has a uniformly hopeless prognosis.

5. Paravenous chains of saccular capillary aneurysms are demonstrated in cases of central vein occlusion and Eales's disease, which simulate those of diabetic retinopathy but, on the whole, differ in the part of the capillary affected, the location in the retina, and their general appearance.

6. A technique is described for producing a picture in animals which clinically simulates central vein occlusion and pathologically exhibits vein thrombosis and venous capillary aneurysms.

The Johns Hopkins Hospital (5).

* See footnote on page 680.

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OCULAR MANIFESTATIONS OF 100 CONSECUTIVE CASES OF MULTIPLE SCLEROSIS*

J. C. YASKIN, M.D., EDMUND B. SPAETH, M.D., AND ROBERT J. VERNLUND, M.D.
Philadelphia, Pennsylvania

The importance of ocular manifestations of multiple sclerosis has been known for several generations. The disease is discussed in varying detail in the standard textbooks of neurology and ophthalmology, and there have been many valuable contributions from various clinics within the last few decades.[1-17]

The diagnosis of multiple sclerosis, with or without ocular manifestations, is at times difficult. It should be recalled that the lesions in multiple sclerosis are disseminated and that this disease can and does mimic many other neurologic conditions.

Furthermore, it is a disease that may develop very insidiously, so that it is not unusual for even an experienced neurologist to diagnose hysteria in the early stages of multiple sclerosis. Moreover, it is to be recalled that this disease, which seemed to be rare in this country four decades ago, is progressively on the increase.

Finally, it is to be remembered that, in view of the unsatisfactory therapy of this condition, the diagnosis should be made with much caution; and that every condition amenable to treatment should be carefully excluded before arriving at this unhappy diagnosis. Some conditions too readily diagnosed as multiple sclerosis may be found later to be cases of brain tumor, arachnoiditis, and, in cases without ocular involvement, a variety of spinal-cord lesions amenable to treatment, such as pernicious anemia and/or spinal-cord tumors.

On the other hand, because of the common occurrence of ocular changes, some cases of multiple sclerosis were early misdiagnosed as brain tumors and some underwent surgical exploration.

Although the literature on this subject is quite extensive, it was deemed advisable to review the ocular manifestations of 100 consecutive cases of multiple sclerosis which were intensively studied by the services of ophthalmology and neurology in the wards and the private services of the Graduate Hospital from 1943 to 1950. Out-patient cases were excluded. It was felt that the included cases were not only carefully studied but were still remembered as individual patients by the investigators. This would permit a more objective evaluation. Indeed, nearly all of the patients were seen by the two senior authors of this paper.

ANALYSIS OF MATERIAL

In addition to routine ophthalmic and neurologic studies, each patient had routine X-ray studies of the skull, the cervical region, and the chest; neuro-otologic studies; spinal fluid studies; and routine chemical, hematologic, and other laboratory procedures. In addition, most of the cases had an electroencephalogram, a gastric analysis, and some of the cases had the benefit of myelography and air studies.

Of the 100 studied cases, 27 had ocular manifestations as the earliest presenting complaint. Of the total number of cases, 56 had ocular abnormalities at the time of the hospital study (tables 1 through 7).

1. *Age and sex incidence.* In the 100 patients examined, 57 were females and 43 were males. The age incidence was as follows: At the time the diagnosis was made—females, 30.1 years; males, 36.8 years. At

* From the Departments of Ophthalmology and Neurology, The Graduate School of Medicine, The University of Pennsylvania, and the Graduate Hospital, The University of Pennsylvania. Presented before the Section on Ophthalmology, the College of Physicians of Philadelphia, April, 1950.

the time of the first symptoms appearing—females, 28.6 years; males, 29.08 years.

2. *First recorded manifestations.* In the 100 cases examined, 73 had, as their earliest manifestations, predominantly general neurologic symptoms; and 27 had ocular symptoms exclusively.

TABLE 1

AGE AND SEX INCIDENCE

	Females	Males	Percent of 100 Cases
Cases with ocular manifestations			56
Sex incidence	57%	43%	
First symptoms (average age)	28.6 yr.	29.1 yr.	
Diagnosis of multiple sclerosis (average age)	30.1 yr.	36.8 yr.	

It may be of interest to enumerate some of the neurologic complaints in cases in which the ocular symptoms were not in evidence. Most of these were related to difficulty in locomotion and to numbness in various parts of the body. Thus, 33 percent of the patients complained of weakness of the lower extremities and of difficulty in walking. Those who complained of weakness of the lower limbs had this impairment: eight were in one limb and nine in both limbs; numbness of the lower limbs was present in 14 cases, nine in one limb and five in both limbs; numbness in the upper limbs occurred in nine cases, four on one side and five on both sides.

Other presenting symptoms included vertigo, tingling in the limbs on stooping, shaking of the hands, difficulty with speaking, sphincter disturbances, and other symptoms referable to the brainstem functions. An occurrence of particular interest as a first manifestation was hemiplegia in two cases and hemi-anesthesia in two other cases. Lastly, a good many patients had as a presenting symptom nervousness closely simulating hysterical conversion symptoms.

Of the 100 cases, 27 patients had ocular manifestations as the first sign of the disease. These may be summarized as follows: Blurring or loss of vision in 16 cases—of these one eye was involved in eight cases, and in six cases the second eye became involved at a later date. In five patients there was almost complete blindness in one eye, and the loss of vision was gradual in two cases. Double vision was complained of as an initial symptom in seven patients, and difficulty in focusing in one patient.

3. *Time interval between the initial ocular symptoms and other evidences of multiple sclerosis.* In patients in whom the ocular manifestations were the earliest evidences of multiple sclerosis, it was possible to determine the interval between the ocular symptoms and other evidences of multiple sclerosis in 20 patients of a total of 27 cases with such symptoms. In these, four had an interval of less than one year; in seven the interval was about one year; in five it was about two years; and in four it was from 10 to 14 years. The average period was one to three years and seven months.

TABLE 2

TIME FROM FIRST EYE SYMPTOM TO NEXT MANIFESTATION OF MULTIPLE SCLEROSIS IN 20 CASES

Length Time (years)	No. Cases
Less than one	4
About one	7
About two	5
10 to 14	4
Average time 3 yr.–7 mo.	

4. *Ocular manifestations at the time of the hospital study.*

a. PUPILLARY CHANGES occurred in 12 out of the 100 cases. Of these, six showed anisocoria, six showed poor reactions to a direct light stimulus, and one case showed no reaction to such a stimulus.

b. EXTRAOCULAR PALSIES occurred in 12 patients. Of these, an external rectus muscle palsy was found in one eye in three cases and the same involvement, bilaterally, in one case. The internal rectus muscle was in-

volved bilaterally three times; and the inferior rectus muscle was involved unilaterally in one case. There was an incomplete unilateral third-nerve palsy in two cases. There were three cases of paralysis of conjugate gaze; in one a paralysis of both right and left gaze, and in two there was paralysis of lateral gaze to one side only. Blepharoptosis was found bilaterally in one case and unilaterally in one case. A Horner's syndrome was found in only one case.

c. A DISTURBANCE IN CONVERGENCE was found in seven cases. This varied in intensity from mild insufficiency to a complete absence of convergence.

d. NYSTAGMUS. At the time of the study in the hospital, 34 patients had nystagmus. Horizontal nystagmus in eyes to the front was found in two cases; 22 cases had horizontal nystagmus on lateral gaze; eight cases had vertical and horizontal nystagmus; one case had rotary nystagmus in all directions; and one case had a coarse horizontal and vertical nystagmus in all directions of gaze. No cases were recorded of a pure vertical nystagmus.

e. ACUITY OF VISION, with best correction. This could not be the measurement of either the poorest or the best vision in the patient, simply a finding of impaired vision at one or more times.

VISION	CASES
Total blindness, O.U.	1
Hand movements, R.E. only	1
3/60, L.E. only	2
6/60, O.U.	1
6/30, R.E. only	1
6/30, L.E. only	2
6/22, R.E. only	1
6/15, O.U.	4
6/12, L.E. only	2
6/9, R.E. only	1
6/9, L.E. only	2

In all other cases, the visual acuity at the time of the examination was without significance.

f. CHANGES IN THE FUNDI. The changes in these cases as noted were limited to the optic-nerve disc and this occurred in 51 of the 100 cases.

In 31 cases there was a diagnosis of retrobulbar neuritis; 14 of these patients had retrobulbar neuritis as the initial sign or symptom of the disease. Of those with initial retrobulbar neuritis, eight patients had one eye involved; six patients had the second eye involved later; and five patients had an almost complete blindness of one eye during the period of the retrobulbar neuritis.

In these 14 patients, 11 cases had disc changes; six cases had both discs involved and three showed normal discs. Temporal pallor was seen in three cases in one eye and in three cases in both eyes.

Optic atrophy, stated as that, was present in one case in one eye, and in three cases in both eyes. Two cases, in single eyes, showed a postpapillitic atrophy.

TABLE 3

FUNDUS FINDINGS

Change	No. Cases	One Eye	Both Eyes
Optic disc, present in 90% of cases with eye signs	51		
Temporal pallor	31	14	17
Diffuse pallor	8	7	1
Definite optic atrophy	9		9
Postpapillitic atrophy	2	1	1
Papillitis or papilledema	2	1	1

There were 17 patients in whom the retrobulbar neuritis was not the initial symptom noted. There were optic-nerve disc changes in 14 of these cases; temporal pallor in one eye, three cases; in both eyes, five cases; temporal atrophy, bilaterally, in one case; optic atrophy, all bilaterally, in two cases; general pallor in one eye, in one case; in both eyes, one case; and papillitis in one case. Two cases had normal fundi.

Temporal pallor was noted in 31 patients; of these it was unilateral in 14 cases and bilateral in 17 cases. Diffuse pallor of the optic discs was noted in eight patients; of these, it was unilateral in one case, and bilateral in seven cases. Definite optic atrophy was noted in nine patients, all bilateral. Postpapillitic optic atrophy was

noted in two patients, one was unilateral and one was bilateral. Papilledema was diagnosed in two cases; both cases were unilateral. One of these cases was profoundly hemorrhagic.

g. FIELDS OF VISION. Eighteen patients in the 100 cases presented definite field changes; seven cases showed a definite central scotoma; one case a paracentral scotoma; two cases showed bilateral central scotomas; and 10 patients showed generalized field contraction, and in six of these cases this was in one eye only. It should be noted that 12 of the 100 patients could not have the fields of vision examined because of the patients' inability to cooperate with that examination.

TABLE 4

VISUAL FIELD FINDINGS

Change	No. Cases
Field change found at some one examination	18
Definite central scotoma (bilateral)	7
Relative paracentral scotoma (some cases suggested past scotomas)	1
Generalized field contraction	10
(one eye only)	6

OTHER STUDIES. It should be stressed that these 100 cases were diagnosed as cases of multiple sclerosis, not only because of the ocular findings but because of additional convincing neurologic manifestations of the disease. In all of them the head X-ray studies were negative. Forty-eight patients had the Bárány tests; of these, 29 gave normal findings; 15 cases, however, showed evidences of infratentorial disease, and supratentorial disease was noted in four cases.

The spinal-fluid studies were performed on 82 patients. The counts in the Wassermann and cell studies were within the normal on all patients studied. A colloidal gold curve abnormality was noted in 23 cases, and the protein was over 60 mg. per 100 cc. in 26 cases. The gastric analysis was negative in all points. This was done routinely to eliminate the central nervous system symptoms usually present in a primary anemia.

The electro-encephalogram was reported in 35 cases; 27 of these studied were normal, four showed slight abnormalities, and in four cases there were borderline findings.

Spinal myelography was performed in 26 cases. All cases were either normal or showed the presence of a pathologic condition of the vertebral disc in the lumbar region which were not relevant to the diseased process. One patient with predominantly lower extremity symptoms had had a laminectomy, with removal of the vertebral disc, which did not change the course of her disease.

Pneumo-encephalogram was performed on nine patients; of these, four cases showed cortical atrophy, and five cases were reported as normal. No ventriculograms were performed in any instance.

One patient was subjected to a cranial exploration at another hospital because of rapidly progressing optic atrophy. This patient will be reported in detail in the discussion.

The routine laboratory procedures, including the hematologic studies, revealed no definite abnormalities except that a few cases had a mild secondary anemia.

COMMENT

The analysis of these cases permits the well-established observation of ocular disturbances in multiple sclerosis, brings into sharp relief less common occurrences, and emphasizes the importance of a differential diagnosis from conditions better amenable to treatment than multiple sclerosis. It is deemed advisable to discuss the findings, at this time and place, in greater length.

1. *Age and sex incidence.* The age incidence is of some importance. Until recent years, multiple sclerosis was assumed to have occurred in individuals before the end of the fourth decade, and most commonly in the third decade. Unfortunately, the onset of multiple sclerosis is seen in rather young people under the age of 20 years, and it is

now known that multiple sclerosis may develop after the fourth decade. Both the age and sex incidence of this series is in keeping with the older observations of Adie.[18]

2. *First recorded manifestations.* Neurologists are all too familiar with the plesiomorphous manifestations in early multiple sclerosis. Every experienced neurologist has made a diagnosis of hysteria in the early stages of multiple sclerosis at one time or another in his life, and sometimes even after many years of experience. The same is undoubtedly true of the ophthalmologist.

General blurring or loss of vision, jumping of vision, and difficulty in focusing are common symptoms in ophthalmic practice, and may be due to a great variety of causes. These include such situations as acute accommodation spasms and failure, acute and chronic eye strain from ocular fatigue, disturbances in binocular single vision from oculomotor imbalance, migraine, and other types of headache, even gastrointestinal upsets seem to have visual disturbances, though these are probably migraine.

On the other hand, it is to be recalled that there may be mild changes in the retina in early multiple sclerosis to produce vague symptoms. Thus, Nielson,[19] speaks of oscillopsia of vision in which condition the patient sees objects swimming as though looking through disturbed water or heat waves. This may be the result of partial atrophy of the optic nerve.

Bricker and Franklin[20] described abrupt attacks of visual impairment consisting of shimmering and the presence of multiple dark areas, and spasms of retinal arterioles, visible on ophthalmoscopic examination. The inhalation of amyl nitrite abolished both spasm and visual inpairment. Rucker[21] believes that some of the bizarre disturbances of vision may be due to these minute vessel changes in the retina in the course of multiple sclerosis.

Diplopia, whether accompanied by an extraocular palsy or not, is a difficult etiologic problem. It is dangerous to make a diagnosis of multiple sclerosis when diplopia is an initial symptom. In connection with this condition one must and should think of lues, early space-taking lesions, infections, myasthenia gravis, thyrotropic exophthalmos, and intraocular space-taking lesions.

The extraocular motor paralyses are either supranuclear, nuclear, intranuclear, or infranuclear. The differential diagnosis of one from the other frequently also indicates the etiology in the case under consideration. Multiple sclerosis can cause any type of oculomotor palsy except that seen in infranuclear nerve-trunk conditions.

3. *The time interval between the first ocular manifestations* and the development of other evidences of multiple sclerosis is most interesting. It is well for the clinician to remember that in the young, at least, bizarre symptoms such as unaccountable blurring of vision, jumpiness in vision, difficulty in focusing, and transient diplopia may be early manifestations of multiple sclerosis.

TABLE 5

OCULAR SYMPTOMS AS THE INITIAL MANIFESTATIONS OF MULTIPLE SCLEROSIS

Complaint	No. Cases	One Eye	Both Eyes
Ocular symptoms present (48% of cases with eye signs)	27		
a. Blurring or loss of vision	16	8	2
Second eye later	6		6
Almost blind	5	5	
b. Double vision	7		
c. Gradual loss of vision (no fundus pathol.)	2		
d. Jumping vision (Subj. effect nystagmus?)	2		
e. Focusing difficulty (intangible complaint)	1		

It is equally important not to indicate to the patient that this is the diagnosis because of the danger of causing unwarranted alarm to the patient or to the relatives.

The occurrence of retrobulbar neuritis appears to be a fairly reliable early manifestation of multiple sclerosis, and, as is well known, even a clearly resolved retrobulbar

neuritis remains a threat to the future of the individual patient. The time interval between the initial ocular symptoms and the subsequent development of other evidences of multiple sclerosis must be borne in mind in discussing or considering prognosis in any case.

4. *Ocular manifestations at the time of the hospital study.*

a. PUPILLARY CHANGES. Pupillary changes

TABLE 6

OCULAR MUSCLE MANIFESTATIONS IN 56 OF THE 100 CASES

Manifestations	No. Cases	Percent of Involved Cases
a. Pupillary	12	18
b. Extraocular palsy	12	18
c. Convergence (diminished to absent)	7	
d. Paralysis of conjugate gaze	2	
e. Nystagmus	34	60
horiz. on lat. gaze	22	
vert. and horz.	8	
horz. in eyes front	2	
horz. and vert. all directions	1	
rotary all directions	1	

in themselves are certainly not diagnostic of multiple sclerosis; at best they are only late manifestations of some disease. They may occur in a great variety of conditions other than multiple sclerosis, both in local conditions of the eye and as nervous-system diseases, especially syphilis, toxic states, and less frequently in brain tumors. Even an Argyll-Robertson pupil has been reported in multiple sclerosis as in other structural diseases of the brain stem.[23]

b. EXTRAOCULAR PALSIES are not a common nor prominent finding in multiple sclerosis. Their diagnosis presents difficulty only when they occur as an isolated initial finding.

c. A DISTURBANCE OF CONVERGENCE, occurring in the young, as the diminution or absence of convergence should arouse the suspicion of multiple sclerosis. It is much more common in other diseases such as post-encephalitic situations, for example Parkinsonism, and in space-taking brain-stem lesions.

d. NYSTAGMUS has always been regarded as one of the cardinal symptoms of multiple sclerosis and it is indeed one of Charcot's triads. It remains a very important sign of multiple sclerosis regardless of the time or period at which it first appears. In this connection, the following should be stated—that not every poorly sustained oscillatory movement is nystagmus; and the end-position nystagmus of fatigue should not be lightly marked as a convincing evidence of major disease. Further, it should be remembered that, in this age of barbiturates, anticonvulsive agents, and other chemicals, transient nystagmus is not uncommon, and since multiple sclerosis is often accompanied by emotional disturbances, the effects of the use of these chemicals can be readily misleading.

The occurrence of nystagmus in association with labyrinthine irritation, as in the Ménière syndrome (due to a variety of toxic factors), must be remembered. Also one must recall that brain tumors are occasionally diagnosed as multiple sclerosis and, in lesions of the posterior fossa, nystagmus is a striking symptom.

One of the patients in the series was diagnosed as multiple sclerosis and treated for that for four years largely because of nystagmus with some cerebellar signs accompanied by a speech disturbance, only to find at the end of that time that he had a huge meningioma in the right middle fossa extending well into the posterior fossa.

Lastly, it should be recalled that in multiple sclerosis the nystagmus need not be constant. This is also true of some infratentorial space-taking lesions.

e. ACUITY OF VISION. The acuity of central vision depends upon the integrity of the papillomacular bundle. One would hardly expect to find a central scotoma in the presence of 6/5 vision; equally certain is the likelihood that one should find a central

scotoma with an impaired central vision.

A pale nervehead is frequently seen with normal central visual acuity. Gliosis of the papilla is not the same as atrophy of the macular fibers. When atrophy is present, then also central visual acuity is, of necessity, impaired.

Ocular nystagmus impairs central visual acuity, but the acquired nystagmus of multiple sclerosis does not affect central visual acuity to any appreciable amount.

f. CHANGES IN THE FUNDI. The diagnosis of retrobulbar neuritis is usually not a difficult task. The classical statement relative to retrobulbar neuritis, "neither the patient nor the examiner sees anything," while an exaggeration is rather descriptive. Frequently, retrobulbar neuritis occurs and passes on into nervehead atrophy without any changes appearing in the fundus until the nervehead shows this atrophy of the papillomacular bundle. Also, it is not uncommon to have a retrobulbar neuritis, diagnosed as such by certain field changes, develop minimal ophthalmoscopic findings in the fundus suggestive of a true papillitis.

TABLE 7

RETROBULBAR NEURITIS

Present	No. Cases	Percent of Cases with Eye Signs
Retrobulbar neuritis	31	55
As initial sign or symptom	14	25
As episode during course of disease	17	30

The occurrence of retrobulbar neuritis in the course of multiple sclerosis has been known for a long time. Thus, Marcus Gunn[23] found in 233 cases of retrobulbar neuritis that 51 showed symptoms of disseminated sclerosis. Benedict[24] found that 155 cases of 225 cases of retrobulbar neuritis had multiple sclerosis. Lillie[25] found, in 500 cases of multiple sclerosis, that 15 percent of them complained of visual loss as an initial symptom of the disease, and in 40 percent of all cases visual symptoms were reported to be the second or third symptom appearing in the course of the disease.

There can be little doubt that retrobulbar neuritis is almost universally due to multiple sclerosis even though retrobulbar neuritis may precede other manifestations of multiple sclerosis, by days, by weeks, by months, and even by years. It is well to bear in mind that other factors may cause retrobulbar neuritis. Among these should be mentioned paranasal sinus infections,[26] a variety of toxic conditions, as phthalium poisoning, and very likely many other exogenous poisons.[27]

Frank optic atrophy occurs uncommonly in the course of multiple sclerosis and in these cases other possible diseases should be carefully ruled out. Thus, in the experience obtained from this series, unilateral optic atrophy was considered a part of multiple sclerosis but it turned out that suprasellar tumors, tumors of the olefactory groove, tumors of the lesser wing of the sphenoid, and chiasmal arachnoiditis were more commonly the cause of such an atrophy.

Even bilateral optic atrophy may occur, however, in the course of multiple sclerosis. One such patient (A. S.) had developed, at the age of 20 years, severe loss of vision bilaterally within a period of three months and, because of bilateral optic atrophy, a craniotomy was done, at another hospital, with essentially negative results.

The patient remained almost completely blind and was followed in the out-patient clinic as a probable case of multiple sclerosis. At the age of 29 years, the patient lost vision in both eyes for two weeks, and developed a hyperthermia for which no adequate cause was found. The autopsy in this case showed an old focus at the chiasm and also an acute demyelinating process consisting of many foci confined to the white matter in the brain, brain stem, and cerebellum. The pathologic diagnosis was multiple sclerosis with recent acute foci.

While retrobulbar neuritis and optic atrophy are the usual ophthalmoscopic

abnormalities in the course of multiple sclerosis, the swelling of the disc may occur. Thus, Nettleship[28] observed cases of swelling of the optic disc in multiple sclerosis. Paton[29] reported three cases of swollen discs.

The presence of a swollen disc in cases of suspected multiple sclerosis should be carefully evaluated in order to avoid grave errors in diagnosis. One of us had one patient who had a combination of retrobulbar neuritis, later followed by papillitis. This case had ultimately frank papillitis, unilateral, with other signs of a frank optic-nerve neuritis.

Case report

A 24-year-old woman had a family history negative for nervous diseases, and the past history was also negative.

The patient had usual good health until late May, 1949, when she noticed difficulty in lifting her left leg, especially in climbing stairs. Within the next 10 days she noticed a band of hypersensitivity to touch in the lower thoracic area. On May 29th, she had increasing ascending numbness of the left lower extremity—this within one week rising to the left clavicle. There was some associated weakness and incoördination of the left lower extremity.

Within the last few days some blurring of vision developed without diplopia—this especially on doing close work.

On June 20th, the visual fields were normal. On June 23rd, the patient complained of difficulty with the left eye and the fields showed a large central scotoma inferiorly. The patient was discharged on July 1st with a diagnosis of multiple sclerosis, but with normal fundi.

By September 9, 1949, the patient noted a pain on movement of right eye; two days later she had lost most of her vision in the right eye. On September 19th, she was admitted to the Graduate Hospital (figs. 1 to 4).

The pupils were equal, the right pupil reacted more sluggishly than the left to light. The fundus of the right eye showed clear media, a hyperemic disc which was elevated one diopter and with margins blurred, the veins were dilated and somewhat tortuous, no hemorrhages nor exudates seen. The

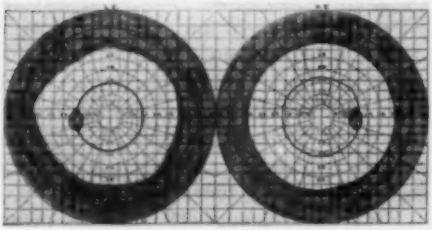

Fig. 1 (Yaskin, Spaeth, and Vernlund). *Case of M. G.* (June 20, 1949.) Left eye: Vision, 6/6. Blindspot, 10-mm. test object; 3/1,000 and 1/1,000. Right eye: Vision 6/5—4. Blindspot, 10-mm. test object; 3/1,000 and 1/1,000.

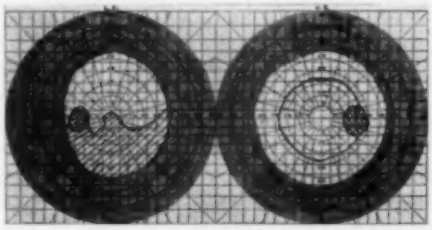

Fig. 2 (Yaskin, Spaeth, and Vernlund). *Case of M. G.* (June 23, 1949.) Left eye: Vision, 1/60. Blindspot, 10-mm. test object; scotoma, 3/1,000. Right eye: Vision 6/5. Blindspot, 10-mm. test object; 3/1,000 and 1/1,000.

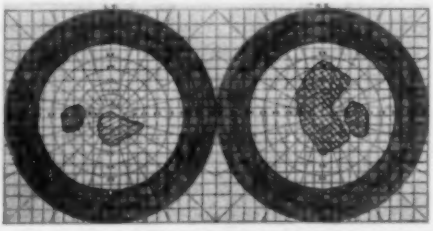

Fig. 3 (Yaskin, Spaeth, and Vernlund). *Case of M. G.* (September 20, 1949.) Left eye: Vision, 1/60. Blindspot, 10-mm. test object; scotoma, 3/1,000. Right eye: Vision: 0.5/60. Blindspot, 20-mm. test object; scotoma, 20/1,000.

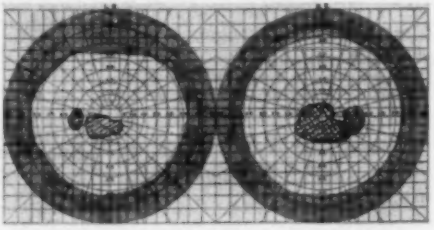

Fig. 4 (Yaskin, Spaeth, and Vernlund). *Case of M. G.* (October 6, 1949.) Left eye: Vision, 6/15. Blindspot, 10-mm. test object; scotoma, 3/1,000. Right eye: Vision, 6/30+2. Blindspot, 10-mm. test object; scotoma, 10/1,000.

macula was clear. In the left eye were clear media, the margins well defined, slight temporal pallor, venous pulsation present, vessels and macula normal.

The fields of vision show an absolute central scotoma and enlarged blindspot, O.D., a relative central scotoma with enlarged blindspot, O.S.

The diagnostic impression was: Optic neuritis, right; retrobulbar neuritis, left.

A fundus examination on October 6th showed: O.D., disc slight temporal pallor; margins, fuzzy and blurred except temporally where they were clear; peripheral vessels and macula normal. O.S., media clear, disc color good, margins sharp, vessels and macula normal. Impression: Subsiding intraocular optic neuritis on right, subsiding retrobulbar neuritis on left.

On October 8th, when the patient was discharged, the scotoma of the right eye had diminished and the vision had improved from 0.5/60 to 6/30. Vision in the left eye, from 1/60 to 6/15.

Another case had a papilledema, with hemorrhages to a marked, in fact to a profound, degree. This patient did not have an increase in the cerebrospinal fluid pressure—hence papillitis was perhaps the truer diagnosis. The significant factor is the rarity of true optic-nerve (bulbar type) involvement.

g. FIELDS OF VISION. The classical findings should be those seen with disease of the papillomacular nerve bundle. The pathology, as seen in the optic pathways, will determine the findings uncovered in the fields of vision, without doubt.

It is well to stress the fact that a negative Bárány test does not rule out the diagnosis of multiple sclerosis. A positive Bárány test, similarly, simply indicates some central nervous-system lesion but does not disclose the nature of that lesion. It is, therefore, not surprising to note, with areas of demyelinization in the cortex and the tracts of the posterior fossa, that the Bárány test should be positive.

The spinal-fluid studies were important largely from the standpoint of the negative findings, and are the means of ruling out, to some extent, other diseases. A positive gold-colloidal curve is at most only suggestive; for it is not pathognomonic of the condition. The pneumo-encephalogram, at the best, is of value chiefly to rule out intracranial space-taking lesions, areas of cortical atrophy, and well-outlined arachnoiditis.

SUMMARY

The ocular manifestations found in 100 consecutive cases of multiple sclerosis were studied by the services of ophthalmology and neurology between the years of 1943 and 1950. This diagnosis was probably correct in a very large percentage of cases.

The correctness, or perhaps certainty, of this diagnosis depended upon many factors. These included: Autopsies, which confirmed and/or eliminated other diagnoses; the continued observation of the cases, over many years (even though the period of hospitalization coverage is from 1943 to 1950, some of the cases have been under observation more than 20 years); and in a few doubtful cases the diagnosis has been confirmed by consultation with other neurologists or ophthalmologists of authority.

Of these cases, 56 had ocular manifestations of multiple sclerosis. Of all these patients, 57 were female and 43 were male. The average age at the onset of ocular symptoms was 28.6 years for the females, 29.08 for the males; and at the time the neurologic diagnosis was made, the average age of the patient was 30.1 years for the females, and 36.8 years for the males.

Ocular manifestations were present as the earliest symptoms in 27 patients. These symptoms varied from such indefinite complaints as general blurring vision (16 cases), jumpiness of vision (two cases), difficulty in focusing (one case), double vision (seven cases), to gradual but progressive loss of vision (two cases).

Other manifestations of multiple sclerosis appeared subsequent to the initial symptoms at intervals varying from a few days to 14 years. Among these 100 patients, 73 presented other subjective neurologic manifestations of tremendous significance in arriving at the neurologic diagnosis.

This portion of the symptomatology, as a

general characteristic of the disease, and its discussion have been deliberately omitted herefrom. This presentation is essentially ophthalmic—hence such an arrangement of possible subject material is logical.

The statement just made, that 73 percent of all cases had other subjective neurologic manifestations of this diseased condition, means that at one time, in the course of the disease, 27 percent of all cases had, at the onset, no symptomatology suggesting the disease except those ophthalmic in nature and character. To the ophthalmologist, this one statement is the outstanding feature in this paper.

The 56 patients who had ocular manifestations during the hospital study of the 100 cases had the following pathologic changes: Pupillary, 12 cases; extraocular palsy, 12 cases; two cases with disturbances in conjugate gaze; seven patients with disturbances in convergence; 34 cases with nystagmus; and 51 cases with significant changes in the optic-nerve discs.

In 31 of the cases, there was retrobulbar neuritis, and of these cases, 14 had retrobulbar neuritis as the initial sign or symptom of the disease. Three patients had a swelling of the optic disc which was diagnosed as papillitis or papilledema.

In 18 cases, there were changes in the fields of vision. Of these, seven cases had a central scotoma; one case had a paracentral scotoma, and 10 cases showed a general contraction of the fields of vision not otherwise accounted for.

The changes in the acuity of vision corresponded with the findings of the optic-nerve discs and with the fields of vision. However, there were some notable exceptions so that some patients whose nerve discs appeared to be quite pale had quite satisfactory acuity of vision. This has been previously discussed.

The Bárány examination, in these cases, was of some help in indicating that an organic lesion existed either above or below the tentorium, even though the Bárány test was negative in a large percentage of cases. This finding of normalcy certainly is significant in arriving at a correct diagnosis.

The electro-encephalogram, other routine laboratory procedures, and the gastric analysis were helpful, even as negative findings when normal. The spinal-fluid studies were rather disappointing in this series of cases, since only a small percentage showed significant changes. The encephalogram, although not diagnostic, may be suggestive, indicating in some cases a degenerative disease of the nervous system. It helped to rule out other structural diseases, such as brain tumor and large areas of cerebral softening.

Conclusions

Despite the unsatisfactory state of the present therapy of multiple sclerosis, rather natural in view of the lack of knowledge of its etiology, an early diagnosis is desirable, at least from the standpoint of prognosis and with the hope that, in the near future, a more satisfactory therapeutic approach may be achieved. Certainly this is not too vain a hope considering the frequent miracles which are occurring through research in antibiotics and their utilization.

The ocular manifestations of multiple sclerosis are frequently early and are always prominent symptoms. These should be carefully evaluated for the purposes of an early diagnosis. At the same time caution must be exercised not to rely too strongly upon ophthalmic symptoms as being pathognomonic of multiple sclerosis. These symptoms are both objective and subjective and include retrobulbar neuritis, nystagmus, oculomotor disturbances, fundus changes, and less clearly defined complaints and objective findings.

It is particularly desirable that conditions which simulate multiple sclerosis be diagnosed at an early time in the course of observation, notably brain tumors, vascular disturbances, arachnoiditis, other inflam-

matory processes, and other degenerative diseases which begin with ocular symptoms, and which are more or less amenable to treatment before the patient becomes hopelessly blind or otherwise disabled.

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IONTOPHORESIS IN OPHTHALMOLOGY*

VERNON L. SMITH, M.D.
Jefferson Barracks, Missouri

The treatment of ocular disease by iontophoresis has assumed increasing importance with the advent of chemotherapy and the antibiotics. Ion transfer of these drugs often serves to introduce them into the globe in concentrations greater than can be obtained by any other method short of actual inoculation.

The purpose of this paper is to review briefly the literature on the theory, technique, and clinical applications of ocular iontophoresis. Particular attention will be given its value in the administration of the antibiotics and sulfonamides.

Historically, iontophoresis has been employed in general medicine for over 100 years and in the treatment of ocular diseases for more than 50 years. Despite this, a large number of ophthalmologists have failed to avail themselves of this valuable aid in therapy.

THEORY OF IONTOPHORESIS

The fundamentals of ionization and electrolysis are well known. An acid, base, or salt when dissolved in water becomes dissociated into positively charged ions and negatively charged ions. An electrical current can be made to pass through this solution by introducing into it the positive pole (anode) and the negative pole (cathode) of a battery. A flow of current between these two poles occurs by virtue of the ionized substances which themselves serve as the conductors of electrons.

Thus, an electropositive ion is attracted to the negative pole (cathode) and an electronegative ion migrates to the positive pole (anode) since like charges repel and unlike charges attract.

For example, in the electrolysis of copper sulfate the electropositive ions of copper are attracted to the cathode and are actually deposited there as metalic copper, while the electronegative ions of the sulfate radical pass to the anode where they react with water to liberate oxygen.

Since the human body is a good conductor of electricity, these same principles may be applied to accomplish therapeutic ion transfer. One electrode may be applied to any point on the body, most conveniently the hands or arm, and becomes the indifferent electrode. The active electrode contained in an eyecup can then be placed over the globe so that a therapeutic solution separates the metal electrode from the cornea. If this solution contains atropine sulfate and the active electrode is positively charged, the positively charged atropine ions will then be repelled from the eye electrode (anode) and attracted toward the negative indifferent electrode. In this manner, the atropine ions pass through the cornea and into the aqueous.

If sodium penicillin solution is placed in the eyecup, the electrodes must be reversed in charge since here it is the negatively charged ion (penicillin) which is of therapeutic value and can only be introduced into the eye by assigning to the active electrode a like charge. The active electrode must then be negative (the cathode) while the indifferent electrode is positive (the anode).

Hence, it is of primary importance to consider the charge of the ion which is to be introduced into the eye and then to assign a like charge to the active electrode.

Von Sallmann[1] has shown that there are other important factors determining corneal penetration of therapeutic ions. Though his conclusions were based on experiments with penicillin and rabbit eyes, it seems permissible to assume that the same principles apply to other solutions.

* Submitted as a thesis for the Postgraduate Course in Ophthalmology, Washington University School of Medicine, Saint Louis.

By comparing aqueous-humor concentrations of penicillin following corneal baths with those determined after iontophoresis, he drew the following conclusions:

If only a corneal bath was used, there was slight, though appreciable, penetration of penicillin into the aqueous. The corneal permeability was increased by previously applied corneal anesthetics or by the previous passage of electrical current through the cornea, both of which apparently injured the epithelium.

If a specific flow of galvanic current was added to a corneal bath, ion transfer resulted in producing concentrations of penicillin in the aqueous which were four to 20 times those following a simple corneal bath. This determination was made by cathode transfer.

It is interesting to note that if the active electrode was made positive instead of negative (he considered the penicillin to behave as a negative ion) there was still some penetration into the aqueous, though only one fourth that attained by cathode transfer. Presumably ion transfer had occurred by diffusion and in spite of the reversed electrical current.

Apparatus required

The essential apparatus necessary for ocular iontophoresis includes a source of galvanic current and some type of active electrode which will keep the therapeutic solution in contact with the cornea. Selinger[2] devised a very satisfactory electrical apparatus which employs batteries and is complete with electrodes and applicators. These are available for purchase.

He describes two types of corneal applicators which are made of lucite. One of these has a contact-lens base with an open chimney extending from its center which serves as a reservoir for the solution. Inside is a platinum loop which acts as the active electrode and is in contact with the solution as well as connected to a source of current. His other applicator is used as an eyecup and has a detachable base so as to be useful for the recumbent as well as the ambulatory patient.

He recommends a rod-type hand electrode which is held by both hands of the patient and serves as the indifferent electrode.

The apparatus supplying the source of current is quite simple and, if desired, can be constructed at small expense. It requires a B battery, an ohm resistor and rheostat, and a milliammeter from which a current of 0.0 to 5.0 ma. can be read.

For clinic work in a hospital, the physical therapy department will be found to have an apparatus capable of delivering the necessary galvanic current. If this facility is available, it is then necessary to procure only the corneal applicator, since any of the conventional moistened arm electrodes may be used as the indifferent electrode. A variety of satisfactory eyecup electrodes may be obtained at the various instrument supply houses.

Technique of ion transfer

Having procured the necessary apparatus, it may be made ready for use in a few minutes.

For the treatment of patients in the office, it is most satisfactory to have the patient seated in a treatment chair with a collapsible back or lying supine on a treatment table.

Some authors suggest that no local anesthetic is necessary; however, it has been shown that their use increases the permeability of the cornea, as well as adds to the comfort of the patient. Pontocaine (0.5 percent solution) is satisfactory.

The source of current is made ready and accessible but is not turned on until all other preparations have been made. The inactive electrode is put in place. If this is of the hand electrode type, the patient may grasp it with both hands. If an arm pad is used, it is moistened and placed under the forearm which rests on the patient's chest.

It is well at this point to reassure the patient as to the innocuity of the procedure, since he may view with apprehension this

array of electrical apparatus to be used on an already ailing eye. At most, there will be a faint, tingling sensation during the actual passage of the current.

The patient's face is directed toward the ceiling and his gaze is fixed on some object. The lids are separated and the empty applicator is placed upon the anesthetized globe with the cornea located centrally. The lids are then allowed to drop over the edges of the applicator. In some cases it may be helpful to insert a lid speculum before introducing the contact electrode.

The therapeutic solution to be used is poured into the chimney of the applicator, which is filled to the brim since there is often some leakage at the base. Gentle pressure in steadying the applicator will minimize this.

Having previously selected the proper charge to be used at the active electrode, the ammeter is set at zero and the switch turned on. No current will flow until the ammeter dial is advanced and this is done slowly until a current of 1.5 to 2.0 ma. is registered. This current is maintained for five minutes and it is usually necessary to readjust the ammeter to keep the flow at the desired level. At the conclusion of the treatment, the ammeter is returned to zero and the switch turned off before any breaks are made in the circuit. This eliminates any spark which might alarm the patient.

Some transient clouding of the cornea may follow each treatment but the patient is reassured that this will clear in a few hours.

No dressing is necessary and the process may be repeated again in 24 hours until four or five courses have been given.

Selinger[2] suggests the use of the eyecup electrode when the contact-lens electrode cannot be employed, as in patients with deformity of the globe or when the patient is excessively apprehensive.

For ambulatory patients, the cup is filled with the solution and is held to the eye as is a conventional eyecup. The solution must be in contact with the cornea so it is necessary that the patient's face be directed upward.

For bed patients, the base of the cup is removed and the cup is held against the eye prior to filling. The use of the eyecup necessarily includes the lids in the therapeutic field and thus may benefit concomitant infections of the lids.

After use, the corneal applicators should be sterilized in 1:1,000 aqueous zephiran.

Drugs frequently used

The following is a list of drugs which have proved useful when administered by iontophoresis. They have been classified so as to indicate the polarity of the active electrode.

Active electrode positive (*Anode transfer*)

Adrenalin hydrochloride	Histamine
Atropine sulfate	Mecholyl
Aureomycin borate	Pilocarpine nitrate
Calcium chloride	Prostigmin bromide
Carcholin	Streptomycin hydrochloride or sulfate
Copper sulfate	Zinc sulfate
Eserine salicylate	

Active electrode negative (*Cathode transfer*)

Bacitracin	Sodium sulfacetimide
Penicillin sodium, potassium or calcium	Sodium sulfadiazine
	Sodium sulfathiazole

In general weak solutions are used. The concentrations employed for some of the more commonly used agents are: adrenalin hydrochloride, 1:20,000; atropine, 0.25 percent; calcium salts, 0.5 percent; pilocarpine, 0.10 percent; streptomycin, 5.0 mg. per cc.; zinc sulfate, 0.25 percent; penicillin, 1,000 units per cc.; sulfonamides, 5.0 percent.

Adrenalin has been used in combination with zinc sulfate and calcium chloride by Erlanger[3] in the treatment of acute infections of the cornea. He advised beginning treatment with zinc-adrenalin iontophoresis for two or three treatments and then using a calcium and adrenalin solution.

A calcium-adrenalin solution is reported by Karbowski[4] as giving excellent relief of photophobia and other subjective complaints when used for patients with vernal conjunc-

tivitis. Symptoms were seen to disappear for from five to 14 days after each treatment permitting a resumption of normal work.

That posterior synechias may often be broken with atropine iontophoresis when all other methods have failed has been shown by Rochat.[5] Further investigation by von Sallmann,[6] who determined aqueous concentrations of atropine and scopolamine in rabbit eyes, yielded significant figures. The aqueous concentrations were found to be six to nine times greater following iontophoresis than could be obtained using corneal baths or subconjunctival injections.

Sulfonamides and antibiotics

The past decade has seen many older methods of treatment fall into disuse because of the efficacy of these drugs. This is not true, however, as regards iontophoresis of the eye. In fact, ocular iontophoresis is now of greater use than ever because it furnishes a method whereby higher intraocular concentrations of these drugs can be attained than when they are administered systemically or by corneal baths.

The recent literature on the subject deals chiefly with experimental results obtained from rabbit eyes. Aqueous concentrations were assayed following various methods of administration of the drug under investigation. Several papers have reported clinically satisfactory results on humans. Experimentally diseased rabbit eyes have also been treated in an effort to evaluate a given drug and method of administration.

Sulfathiazole. In 1941, Bellows and Chinn[7] demonstrated that oral therapy with sulfathiazole provided intraocular concentrations too low to be clinically satisfactory.

The next year Boyd[8] investigated the exact concentrations of sodium sulfathiazole in the cornea, aqueous, and vitreous following corneal baths and following iontophoresis. It was found that administration by iontophoresis provided three to 10 times greater concentrations than did the corneal bath.

A further advantage of iontophoresis over the systemic administration of sulfathiazole is the absence of toxic reactions often seen following oral use of the sulfonamides.

Sulfadiazine. Rabbit eyes experimentally inoculated with various types of pneumococci were found by von Sallmann[9] to respond to treatment much better when sulfadiazine was administered by iontophoresis than when corneal baths were used. He also found sulfadiazine iontophoresis to be of assistance in treating experimental endophthalmitis produced by Staphylococcus aureus and Clostridium welchii.[10]

Sulfacetimide. A particularly interesting paper by von Sallmann[11] was published in 1945 in which he used a solution containing both sulfacetimide and penicillin for iontophoresis of rabbit eyes.

Determinations of the aqueous concentrations were made following iontophoresis for five minutes, when the two drugs were used singly and in combination. He showed that the same concentrations were obtained in the aqueous regardless of their combination, and that the presence of sulfacetimide did not exert any antagonistic effect on the bacteriostatic activity of penicillin in vitro.

A combination of this nature would seem particularly useful in office practice since those organisms susceptible to but one of these agents would immediately be brought under control and much valuable time saved.

An excellent review of the literature has been made by Thygeson[12] on the value of the sulfonamides in the treatment of various eye diseases. Administration by both the oral route and by iontophoresis was considered. He concluded that very rapid and complete healing took place in trachoma, inclusion conjunctivitis, lymphogranuloma, gonorrheal conjunctivitis, and in diseases due to meningococci, influenza bacilli, diplococci, coliform rods, Friedländer's bacillus and pyocyaneus bacilli.

The sulfonamides were found to have little or no effect on brucellosis, tularemia, syphilis, leprosy, sympathetic ophthalmitis,

uveitis, ocular pemphigus and infections due to nonhemolytic or anaerobic streptococci.

He considered local treatment preferable to systemic administration in mild ocular infections because of the toxic effects associated with oral therapy.

Penicillin. It is generally agreed that the systemic administration of penicillin results in very low intraocular concentrations.

Leopold[13] and his associates have shown that the local application of penicillin drops was more effective than the intramuscular administration of penicillin in treating rabbit corneal infections caused by Gram-negative bacilli.

The superiority of penicillin iontophoresis over its application by corneal baths,[1, 14, 15] cotton packs,[14] or subconjunctival injection[14] has been demonstrated by von Sallmann. However, only traces of penicillin were found in the lens and vitreous regardless of how it was administered. He also showed that penicillin iontophoresis was superior to the corneal bath in the treatment of pneumococcal infections[9] produced in rabbit eyes.

Experimental endophthalmitis due to Staphylococcus aureus and Clostridium welchii has been checked with penicillin ion transfer.[10]

That iontophoresis can produce concentrations of penicillin in human eyes, as well as rabbit eyes, that are four to 20 times that produced by corneal baths was shown by von Sallmann.[1]

The clinical advantages of the simultaneous application of sodium sulfacetimide with penicillin by iontophoresis have already been mentioned.[11]

Streptomycin. Very satisfactory intraocular concentrations of streptomycin have been obtained by iontophoresis.

Using rabbits, Leopold and Nichols[16] showed that a considerably greater concentration of streptomycin was found in the aqueous following iontophoresis than when streptomycin was given intravenously, intramuscularly, or in local drops or ointment. In another paper, Leopold[17] demonstrated that intravitreal injections of streptomycin were to be used with caution because they produced retinochoroidal exudation and subsequent degeneration if employed in concentrations greater than 800 μg. per injection.

High vitreous concentrations[12] were attained by the retrobulbar injection of streptomycin 100,000 units per cc. followed by corneal iontophoresis using a corneal electrode filled with saline. In this case the neck electrode was made positive thus driving the streptomycin through the posterior pole of the eye. By this method, concentrations in the vitreous were comparable to those obtained by the direct injection of streptomycin into the anterior chamber.

Streptomycin has been found to be effective in the treatment of experimental infections due to Proteus vulgaris, Pasteurella tularensis, Mycobacterium tuberculosis, and organisms of the Friedländer group.[16]

Grunwell and Schultz[18] obtained encouraging results after streptomycin iontophoresis to patients suffering from corneal ulcers, uveitis, and acute conjunctivitis. They used concentrations of 50 to 100 mg. per cc. applied over the partially closed lids by a pad saturated with the solution. It was felt that these comparatively high concentrations were necessary because of the dilution by the tears and they wished to include the lids in the field so as to eradicate any nidus for infection in the tarsal glands.

Aureomycin. The present status of the intraocular penetration of aureomycin is somewhat controversial and no doubt subsequent investigation should clarify it considerably.

de Roetth[19] used aureomycin borate 5.0 mg. per cc. with cathode iontophoresis, stating that anode iontophoresis caused extensive damage to rabbit eyes. Iontophoresis produced low intraocular levels with possible antibiotic effect and intravenous injections produced slightly higher aqueous levels. He concluded that there was no ocular penetration of aureomycin following corneal baths,

oral or intramuscular administration. He found subconjunctival injections too irritating for clinical use.

In a more recent paper, Bellows[20] and his associates reportedly used aureomycin borate (5 mg. per cc.) for five minutes with a current of 2.0 ma. It is to be noted that, in contrast to de Roetth, who used cathode transfer, Bellows employed anode transfer which theoretically should give higher therapeutic levels. Aqueous concentrations in rabbit eyes were determined following corneal baths, drops, subconjunctival injections, and iontophoresis. It was found that there was no penetration of the intact cornea following corneal baths or drops. However, clinically significant concentrations were produced by corneal baths to abraded or ulcerated corneas.

Iontophoresis to the intact cornea resulted in slight penetration of aureomycin into the aqueous, but iontophoresis was not tried on the damaged cornea, though it would seem reasonable that good penetration could be expected.

Hence, conclusions as to the usefulness of iontophoresis for aureomycin therapy must await the results of further investigations.

Bacitracin. The use of iontophoresis for the introduction of bacitracin into rabbit eyes was given favorable comment by Locke.[21] He used bacitracin (1,000 units per cc.) for five minutes at 1.6 ma. with the cathode to the eye. It was shown that two to three times as much bacitracin could be obtained in the aqueous by iontophoresis as compared with corneal baths. These concentrations were well over that necessary to inhibit most strains of staphylococci.

Summary

1. An attempt has been made to familiarize the ophthalmologist with the practical applications of iontophoresis and to impress upon him the growing importance of this means of therapy.

2. The theory behind the process of iontophoresis was advanced and the apparatus necessary for its application described.

3. The technique for ion transfer in the office and hospital has been discussed and a list of useful drugs and concentrations given.

4. The recent literature was reviewed on the value of iontophoresis in the administration of the various sulfonamides and antibiotics.

Conclusions

1. The use of iontophoresis for the introduction of certain drugs into the eye is based upon sound scientific principles.

2. The selection of the charge to be used at the active electrode varies with the drug employed. This charge must be the same as that of the ion which is to be introduced into the eye.

3. The apparatus required for ocular iontophoresis is both simple and inexpensive.

4. The technique of iontophoresis is easily carried out in the busy office or hospital in but a few minutes.

5. Ion transfer provides a method of introducing high concentrations of many useful drugs into the eye.

6. Posterior synechias which have resisted all other means of treatment may sometimes be freed by iontophoresis with mydriatics.

7. In general, higher concentrations of the sulfonamides and antibiotics can be obtained in the eye by iontophoresis than by any of the other common routes of administration.

8. Sulfathiazole iontophoresis to rabbit eyes resulted in aqueous concentrations which were three to 10 times greater than the concentrations following corneal baths.

9. Sulfacetimide in combination with penicillin can be administered effectively by iontophoresis without diminishing the potency of either.

10. Penicillin ion transfer gave higher aqueous concentrations both in human and rabbit eyes than when the antibiotic was introduced by corneal baths, subconjunctival injection, or cotton packs; however, concentrations in the lens and vitreous were too low to be of value.

11. Streptomycin is particularly effective when introduced by ion transfer. Aqueous concentrations in rabbit eyes were greater following iontophoresis than following intravenous, intramuscular, local drops, or ointment administration.

12. Aureomycin and bacitracin iontophoresis have yielded some encouraging reports but further investigation is necessary to establish their clinical value.

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THE CHRONIC GLAUCOMAS: A SURVEY*

J. P. F. Lloyd, F.R.C.S.
Oxford, England

Attempts to produce an acceptable clinical classification of the so-called primary glaucomas have been fairly frequent in the past, and give a seeming, as it were, of a barometer of contemporary interest in the disease, of developments in clinical methods of examination and treatment, and of periodic steps in fundamental research aimed at elucidating the underlying cause or causes of the condition. It is unlikely, therefore, that an acceptable classification will ever be produced until there can be one which is based upon fully or nearly fully understood factors in causation.

Historically we find von Graefe's[1] attempt probably the earliest, comprising the four groups: acute glaucoma, absolute glaucoma, secondary glaucoma, and "amaurosis with excavation of the disc."

In the first two decades of this century, primary glaucoma had, by more or less mutual consent, come to be subdivided into: acute congestive, chronic congestive, and chronic noncongestive, though even this was opposed later by many redoubtable thinkers who regarded as misleading such subdivision of what they regarded as one disease entity —Elliot,[2] Parsons, May, S. R. Gifford, E. Fuchs, Gradle, and Duke-Elder (quoted by Sugar[3]).

Later, Raeder[4] divided primary glaucoma into two groups according to the measured depth of the anterior chamber. This was modified by Barkan[5] and by Gradle and Sugar[6] to accord instead with the observed width or narrowness of the anterior-chamber angle.

One other twist was introduced by the Elschnig school in the 1930's, the substitution of "compensated" and "uncompensated" for "noncongestive" and "congestive," respectively. This seems to have served little purpose in clarifying the situation.

Next we come to Sugar's[7] excellent attempts to produce a classification in keeping with all aspects of present-day knowledge. The latest version I have seen—he has amended it several times—is shown here in part.

A. Classification of the glaucomas

I. Primary glaucomas

- A. Glaucoma simplex (chronic simple glaucoma)
  - 1. Noncongestive phase
  - 2. Congestive phase (rare)
- B. Glaucomas caused by anatomic and developmental anomalies
  - 1. Congenital glaucomas
    - a. Hydrophthalmos
    - b. Glaucomas associated with aniridia or neurofibromatosis
  - 2. Juvenile glaucoma
  - 3. Acute (narrow-angle) glaucoma—due to anatomic plus physiologic angle-narrowing factors which lead to mechanical obstruction of trabecular spaces by iris. This includes acute glaucoma associated with microcornea
    - a. Noncongestive phase—including "dilatation glaucoma"
    - b. Congestive phase—classical "acute congestive glaucoma" and the recurrent form called "chronic congestive glaucoma" in the older classification

On examining this closely we notice two things:

1. That the bulk of cases (usually known as glaucoma simplex) occupy one heading only; namely, "A" (noncongestive phase), and we know well that these comprise at least 80 percent and probably more of all cases of primary glaucoma, and probably 70 percent or more of all glaucomas, primary and secondary. This defect is, as I have said, bound to occur in any classification based on our present comparative ignorance of the underlying causes of glaucoma, and is so poignantly expressed in the key-word "primary." As shown later, I have myself at-

* From the Oxford Eye Hospital.

tempted to split this group by study of a clinical series, but have not met with any great success in this direction.

2. That under "B. 3 (narrow-angle acute glaucoma)," there is "(a)" a "noncongestive phase" about which, so far as we can see, there is little that can be called "acute."

I have been working for some years myself on the same lines as Dr. Sugar, but have not hitherto (with one exception) got so far as putting my findings in print. Like him, and possibly more so, I have been frustrated by the utter refusal of the large "simplex" group to subdivide in any ordered fashion whatever. There seems one exception to this which will be argued later, under the heading "rapid simplex," as a new subdivision.

TABLE 1

SUMMARY OF ALL CASES

A. No. of cases	167	No. of eyes	334
B. 1. No. of eyes lost when first seen			3
2. No. of eyes blind when first seen			55
3. Nonglaucomatous or nonproven			27
The remainder are included in the survey, and are the subject matter of tabulations			
C. 1. Aphakic			18
2. Capsulocuticulari			4
3. Simplex with thrombosis			3
4. Buphthalmos			5
5. Glaucoma cyclitica			4
6. Glaucoma simplex			215
Total			249

THE SURVEY

My motive in attempting a survey of glaucoma-simplex cases was twofold:

1. I had felt discontented for many years with some points generally accepted and taught. The mains ones were:

a. That, whatever supervision and treatment is undertaken in this disease, there was inevitable slow deterioration in the course of time.

b. That central vision is often lost at operation, especially if field loss has approached very near the fixation point.

c. That the condition commonly occurs in the presence of a normal chamber angle.

I had also determined to search for evidence that the vascular factor in the condition might be a local manifestation of a general disease.

2. I had long wished to see whether the condition could in any way be subdivided into more or less separate types on clinical grounds, failing any immediate prospect of this becoming possible by fundamental etiologic knowledge.

I thought, and still think, the use of the term "chronic" wrong and misleading as applied to congestive glaucoma, and had previously argued this (Lloyd[8]). Likewise, the term "acute attacks" applied to chronic glaucoma seemed a bad one, and the term "subacute glaucoma" the merest evasion and a confession of indecision.

It may be observed in Table 1 that, in arriving at the number of eyes (249) worthy of study from the point of view of clinical behavior, those blind from glaucoma when first seen at Oxford and those lost at this time (58) have been excluded as have also those "second" eyes in which a definite diagnosis of glaucoma had not been made at the time of the survey.

Certain "controversially secondary" cases (39) are included as listed in Table 1. When the results of treatment come to be considered, however, the first group (B) is re-introduced by adding them to the total in a separate column.

As detailed a study as possible of the eligible 249 eyes was then made under the various headings of the tables.

Table 2 shows little more than a rather flat peak between the ages of 50 and 80 years, which is what one would have expected from clinical experience, though the absolute peak at 70 to 74 years is rather higher than that usually given. The first sharp rise at 50 to 54 years corresponds roughly with the menopausal age in women, and is also a common age for the onset of certain manifestations of cardiovascular and vasomotor instability.

Table 3 illustrates the known fact that a

TABLE 2

AGE DISTRIBUTION OF VARIOUS TYPES

(Age (in years)	Total	Simplex	Aphakic	Simplex with Thrombosis	Cyclitica	Capsulo-cuticulari	Buph-thalmos
2	2						2
30–34	4				2		2
35–39	2	2					
40–44	5	4					1
45–49	12	12					
50–54	27	19	2	2	2	2	
55–59	23	21	2				
60–64	33	30	1			2	
65–69	35	34	1				
70–74	44	41	2	1			
75–79	33	32	1				
80–84	18	14	4				
85–89	2	2					
Not stated	9	4	5				
Total	249	215	18	3	4	4	5

proportion of cases with apparently normal anterior-chamber depth may in fact have a narrow angle. The figures correspond roughly to Duke-Elder's[9] estimate of wide angle in 60 percent and narrow angle in 40 percent. That is to say, the width of the angle is probably of little importance in classification as there is at present no related clinical behavior as between cases of glaucoma simplex. Nor does the "rapid" type appear to be related to angle width; 31 gonioscopic records in such cases showed 13 narrow and 18 wide angles.

Table 4 shows, as one would expect, that cupping of the disc is easily the most frequent presenting sign. Tension, with or without congestive manifestations, comes second, and other signs well behind. This emphasizes the advanced stage at which this insidious disease commonly presents itself. The total exceeds the number of eyes because, in some cases, more than one sign was judged to be the presenting sign—for example, cupping and high tension.

It is, I think, surprising that diagnosis (table 5) was apparently considered to be confirmed on less than three factors in as many as 53 eyes. This may be due to inadequate records, but my feeling is that this grave diagnosis should rarely be made unless either the three cardinal signs are present, or less than three of them are found in association with potent other considerations—for example, onset of congestive phase, very high tension (35 mm. Hg (Schiøtz) or over), presence of the disease in the other eye, and so on.

This instructive Table 6 illustrates to my mind the lack of any definable relation be-

TABLE 3

RELATION OF ANTERIOR-CHAMBER DEPTH AS RECORDED AND ITS RELATION TO ANGLE WIDTH AS OBSERVED BY GONIOSCOPY

Shallow anterior chamber	77
Shallow periphery type	28
Normal or deep	133
Not stated	11
Total	249

Gonioscopy	Shal-low	Shal-low Periph-ery	Normal Depth
1. Narrow angle, actual or potential mechanical closure	18	12	9
2. Open angle—apparent plastic closure	17	15	48
3. Congenital-type vascular tissue present	—	—	8
4. Wide-open angle pigmented	—	—	6
Total	35	27	71

TABLE 4

RELATIVE FREQUENCY OF PRESENTING SIGN*

Tension (including terminal cases)	86
Cupping	144
Field loss	7
Others	7
Insufficient record	10
Total	254

* The three cardinal signs regarded as being: (1) Tension, (2) cupping, (3) field loss.

TABLE 5

SIGNS ON WHICH DIAGNOSIS WAS CONFIRMED

Tension, cupping, and field loss	103
Any 3 or more of the 5 factors*	79
Less than 3 of the 5 factors	53
Insufficient record	14
Total	249

* Factors: (1) Tension, (2) cupping, (3) field loss, (4) other considerations, (5) gonioscopy.

TABLE 6

RELATIVE INCIDENCE OF VARIOUS COMBINATIONS* OF CONFIRMATORY SIGNS

Tension + cupping	142
Tension + field loss	114
Cupping + field loss	153
Tension − cupping	33
Cupping − tension	58
Tension—field loss	61
Field loss − tension	48
Cupping − field loss	47
Field loss − cupping	9
Insufficient records	14
Total	679

* + = with.
− = without.

tween the three cardinal signs. As might be expected, cupping with field loss is rather the more frequent, but the general impression is one of absence of any regular behavior characteristics, rather reminiscent of some of the higher propositions of physics. The nine alleged cases of field loss without cupping suggest the need for more careful campimetry.

The third figure in Table 7 is interesting as it implies a much higher frequency of "low-tension glaucoma" (Schnabel's cavernous atrophy), "sclerotic atrophy of the optic disc" (Duke-Elder[10]), than is normally realized—over 21 percent of 249 eyes. The corresponding incidence of cupping does not appear to give any useful information.

TABLE 8

OBSERVATIONS OF "RAPID" OR "TERMINAL" CASES

	Cupping Present	Cupping Absent
Field loss—present	25	2
Field loss—absent	8	11
Total		46

As explained elsewhere in the text, the class summarized in Table 8 is distinguished by:

1. Evidence of prolonged continuously high tension without entering a congestive phase, or before doing so (true acute glaucoma).

2. Marked lack of response to miotics (table 9).

TABLE 7

RELATION OF TYPE OF TENSION TO PRESENCE OR ABSENCE OF CUPPING

	Cupping Present	Cupping Absent	Insufficient Record	Total
1. Continuously above 30 mm. Hg (Schiøtz)	77	20	1	98
2. Intermittently above 30 mm. Hg (Schiøtz)	58	13	1	72
3. Never above 30 mm. Hg (Schiøtz)	47	2	4	53
4. Insufficient record.	18		8	26
Total				249

3. These features may be associated with either a wide or narrow chamber angle. As may be seen, they also show a high (but not exclusively so) rate of cupping. Again two cases alleged to have field loss without cupping are of doubtful value.

In four of the 249 cases no record of miotic therapy was found. Table 9 shows that 69 out of 199 "ordinary," that is, non-terminal, eyes were controlled—more than one third—but of 46 rapid terminal cases only four responded.

The fourth and fifth figures in each column of Table 9 show the indications on which surgery was undertaken (or advised). It may be seen that, in the overwhelming majority, persistent high tension was the deciding factor, and this of course is in accordance with current ideas. One would, however, wish to see more emphasis on careful campimetric control (Lloyd[11]).

Table 10 represents an attempt to see whether any relation exists between miotic response and depth of anterior chamber. Its value is of course vitiated somewhat by the known possibility of narrow angles occurring in deep anterior chambers.

As regards tension, the findings may be summarized as follows:

In the terminal cases, tension was controlled in three, but not in 27 presumable narrow angles; tension was controlled in

TABLE 9

RESPONSE TO MIOTIC THERAPY AND INDICATION FOR OPERATION

	Terminal Types	Other Types
Tension controlled+field loss prevented	4	69
Tension alone controlled	—	22
Field alone controlled	37	91
Tension not controlled	42	109
Field loss not controlled	4	40
Insufficient record	—	3
Total	87	334

TABLE 10

RELATION OF MIOTIC RESPONSE TO RECORDED DEPTH OF ANTERIOR CHAMBER

	Terminal Eyes				Other Eyes			
	Shallow A.C.	Shallow Peripheral A.C.	Deep A.C.	Insufficient Record	Shallow A.C.	Shallow Peripheral A.C.	Deep A.C.	Insufficient Record
1. Tension controlled	3	—	1	—	23	11	55	1
2. Field controlled	19	8	13	1	42	17	93	7
3. Tension not controlled	19	8	14	1	31	9	60	9
4. Field not controlled	2	—	2	—	12	3	22	3
5. Refused operation	1	—	—	—	—	—	—	—
6. Insufficient record	—	—	—	—	1	—	3	—

TABLE 11

RELATION OF MIOTIC RESPONSE TO GONIOSCOPIC FINDINGS WHERE AVAILABLE

	Terminal Eyes				Other Eyes				
	Mechanical Closure of Angle	Plastic Adhesive Closure of Angle	Open Angle	Total	Mechanical Closure of Angle	Plastic Adhesive Closure of Angle	Congenital Vascular Tissue in Angle	Open Angle	Total
1. Tension controlled	1	1	1	3	21	32	5	4	62
2. Field controlled	10	11	1	22	26	58	7	5	96
3. Both tension and field controlled	1	1	1	3	20	27	4	4	55
4. Tension not controlled	10	12		22	7	35	3	1	46
5. Field not controlled	1	2		3	2	9	1		12
6. Tension or field not controlled	11	14		25	9	44	4	1	58
7. Refused operation	1			1		1			1

TABLE 12

ANALYSIS OF OPERATIONS PERFORMED

	Aphakic						Others							All Operations						
	Trephine	Iridencleisis	Iridectomy	Cyclodialysis	Sclerotomy	Total	Trephine	Iridencleisis	Iridectomy	Cyclodialysis	Sclerotomy	Goniotomy	Total	Trephine	Iridencleisis	Iridectomy	Cyclodialysis	Sclerotomy	Goniotomy	Total
Number performed	5	5	6	4	—	20	124	39	13	8	3	2	189	129	44	19	12	3	2	209
Satisfactory drain.	2	2	—	1	—	3	76	16	3	4	—	—	99	78	18	3	5	—	—	104
Satisfactory drain.; macula became degen.	—	—	—	—	—	—	5	5	1	—	—	—	11	5	5	1	—	—	—	11
Unsatisfactory drain. control. on miotics	2	2	3	1	—	8	15	8	5	1	1	—	30	17	10	8	2	1	—	38
Unsatisfactory drain. controlled by miotics, macula became degen.	—	—	1	—	—	1	1	1	1	—	—	—	3	1	1	2	—	—	—	4
Total controlled	4	4	4	2	—	14	97	30	10	5	1	—	143	101	34	14	7	1	—	157
Satisfactory drain., but deterior.	—	—	—	—	—	—	4	1	—	—	—	—	5	4	1	—	—	—	—	5
Unsatisfactory drain., operation repeated	1	1	1	1	—	4	17	6	—	3	2	—	28	18	7	1	4	2	—	32
Unsatisfactory drain., consequent deterior.	—	—	1	1	—	2	5	2	3	—	—	—	10	5	2	4	1	—	—	12
Unsatisfactory drain., consequent deterior., macular degen.	—	—	—	—	—	—	1	—	—	—	—	—	1	1	—	—	—	—	—	1
Total not controlled	1	1	2	2	—	6	27	9	3	3	2	—	44	28	10	5	5	2	—	50
Not followed up	—	—	—	—	—	—	—	—	—	—	—	2	2	—	—	—	—	—	2	2
Was second or subsequent operation in	—	—	—	—	—	—	—	—	—	—	—	—	—	8	11	2	8	1	2	32

one, but not in 14 presumable wide angles.

In other cases, tension was controlled in 34, but not in 40 presumable narrow angles; tension was controlled in 55, but not in 60 presumable wide angles.

In other words miotic control rate of tension seems to bear no real relation to anterior-chamber depth.

The field control rate, which is much higher, seems also to lack detectable relation to anterior-chamber depth.

Table 11 attempts to make up for the shortcomings of Table 9 by summarizing miotic response in cases in which actual gonioscopic records were available.

In the terminal cases, the disease was controlled in one, but not in 11 narrow angles; the disease was controlled in two, but not in 14 wide angles.

In the other cases, the disease was controlled in 20, but not in nine narrow angles; the disease was controlled in 35, but not in 49 wide angles.

The total of these two groups shows, as would be expected, a significantly higher control rate in the presence of a narrow angle, especially if the eye is not in or near a congestive phase, when, presumably, irreversible adhesive changes commence in the angle.

It is interesting to study Table 12 at length, as it shows a more or less uniform success-rate as between the three operations —trephination, iridencleisis, and iridectomy —of approximately three quarters of the total in each case. The number performed of the other three operations is too small for any considered conclusions, though the low success rate of cyclodialysis is notable, and may possibly be due to lack of technical experience of the procedure.

It should be noted that the total of 50 eyes not controlled should have subtracted from it the 32 in which there was a second or subsequent operation, leaving the agreed total of 18 cases which were never stabilized.

I think this supports the tenet that one should not hesitate to embark on further surgery when, for any reason, the results of the first operation are not entirely satisfactory. To fail to do so is to deny that there were proper indications for performing an operation in the first place. These results are discussed further under Table 14.

TABLE 13

GONIOSCOPIC RECORDS AVAILABLE IN OPERATION CASES

	Trephine	Iridencleisis	Iridectomy	Cyclodialysis	Total
No. performed					
Wide angle					
Satisfactory drainage	20	3	—	2	25
Unsatisfactory drainage	13	5	—	2	20
Narrow angle					
Satisfactory drainage	9	5	—	—	14
Unsatisfactory drainage	5	—	—	—	5

The high number of trephinations performed is probably normal for this country, though one would like to see a larger proportion of other operations included in a future series.

I thought Table 13 might be of interest, though unfortunately the number of gonioscopic records available is small. The only possibly significant figure here is the high proportion of successful iridencleises in the presence of a narrow angle, though the numbers are, of course, small.

There are two points of interest in Table 14.

1. The very high proportion of subsequent lens changes occurring in a quarter to a third or more of all cases of each type of operation.

TABLE 14

COMPLICATIONS OF SURGERY

Number of operations	Trephine 129	Iridencleisis 44	Iridectomy 19	Cyclodialysis 12	Total
None noted	—	—	—	—	111
1. Immediate infection	—	—	—	—	1
2. Persistent choroidal detach.	—	—	—	—	3
3. Persistent loss of A.C.	—	—	—	—	2
4. Significant iridocyclitis	—	—	—	—	5
5. Loss of eye	—	—	—	—	4
6. Subsequent thrombosis of retinal vein	—	—	—	—	6
Subsequent lens changes	38	13	5	5	61
Subsequent macular degen.	7	6	3	—	16
					209

2. The fact that, though far behind in frequency, subsequent macular degeneration is the second most frequent complication in glaucoma surgery. This is a thing I have suspected for many years, but have never found mentioned in the literature on the subject. I think it possible that the frequency of macular failure may account for the tradition already mentioned that central vision may fail as a result of surgery in eyes with advanced field loss. I certainly could not find any evidence of any other factor which could have given rise to this tenet.

Both these complications are extremely important, as there is no doubt that they are a potent source of the gloom with which glaucoma surgery is commonly viewed: "Only those who do not follow up their cases carefully are optimistic regarding the surgical treatment of glaucoma" (O'Brien and Weih[12]).

It is all very well to stabilize the glaucoma process, and this can undoubtedly be done in a very high proportion of carefully observed cases (table 15). From the patient's point of view the result can hardly be considered a satisfactory one if vision, especially central vision, is materially or grossly impaired by extensive lens changes, or by complete macular failure.

Again it must be remembered that some of these cases were stabilized with the restricted field or depressed central vision with which they first presented themselves. This does not in any sense imply a restoration to a normal or near normal state of affairs.

The stabilization results shown here are quite encouraging, and rather higher than

TABLE 15

STABILIZATION SUMMARY

	Of 177 Eyes Operated		Of 249 Eyes Studied		Of 307 Eyes (334 Less 27 Non-glaucomatous)	
	No.	Percent	No.	Percent	No.	Percent
Stable on miotics to date			73	29.3	73	23.8
Stable after one or more operations with miotics	42	23.7				
Stable after one or more operations without miotics	115	64.9				
Total stabilized after surgery	157	88.6	157		157	51.11
Not followed up	2	1.2				
Never stabilized	18	10.2	18	7.2	77	25.1
Total second or subsequent operation	32					
Grand total stabilized			230	92.4	230	74.9
Refused operation			1	0.4		

those usually quoted (Duke-Elder[13]); 88.6 percent of all eyes submitted to surgery is notable, but is of course subject to the rather less encouraging proviso made above.

Another notable figure here is that of 92.4 percent of eyes which were considered treatable when first seen—that is, were not blind or absent—compared with 74.9 percent when all cases are included; namely, blind or absent when first seen, sometimes with and sometimes without treatment elsewhere.

Hg (Schiøtz), owing to refusal of operation, for over two years before the disc appearance became even suspicious of abnormality.

We must also remember, however, the comparatively large number of cupped discs in the series in eyes showing no recorded rise in tension.

This led me to suspect that in many such cases the tension had been continuously high for a long time before the appearance

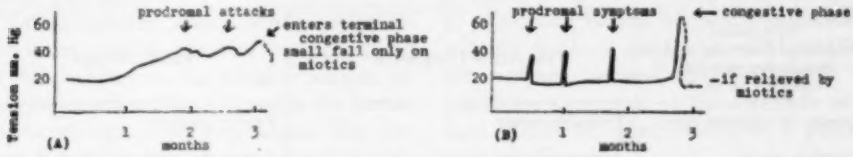

Fig. 1 (Lloyd). Tension behavior in rapid simplex glaucoma and in true acute congestive. (A) Rapid simplex. (B) True acute congestive (Sugar's conception). Note: Theoretically, the tension behavior prior to presentation at the hospital is one of the important differences between the two conditions. Too often, there is no definite means of ascertaining this. However, on occasion, I have had such cases under observation prior to and during their entrance into the terminal congestive phase.

I think this emphasizes the desirablility of timely diagnosis, with adequate and detailed supervision in this disease. The close attention necessary for these cases can probably only be achieved in a conscientiously run clinic specially set aside for the purpose.

Conception of rapid or terminal glaucoma simplex

When studying a previous series (Lloyd[14]) I found myself repeatedly puzzling over cases which, although bearing the label "acute or subacute congestive glaucoma," did not by any means appear to fit the accepted description. The visual damage was often far in excess of the time during which the condition was stated to have existed, as was likewise the evidence and degree of cupping of the optic disc.

A majority of discs at least will stand high tension for periods of weeks, if not months, before cupping appears. To quote one case only in the present series, recorded tension in the right eye varied from 35 to 45 mm.

of the congestive phase for which the patients had presented themselves at the hospital, and that the condition had most of the features of glaucoma simplex, with the exception that continuous high tension and ultimate circulatory breakdown into a congestive or terminal phase were occurring much more rapidly, that is, in a few weeks, than is usual in simplex (fig. 1).

The clinical picture presented on attending the hospital is often indistinguishable from a mild acute glaucoma unless one is aware of possibilities. In fact, the differentiation may be impossible until tension has been reduced by medicine or surgery to an extent where the state of the disc and the visual fields can be assessed. My attempted differentiation is tabulated in Table 16.

We may ask ourselves whether the differentiation shown in Table 16 is important. After all, the clinical situation is more or less common to both types, and the primary aim of the treatment is identical in either condition—the normalization of tension by

medicine or surgery at the earliest practicable moment.

I am sure, however, that there is a strong case here for advocating the iridencleisis operation in all cases where there is any doubt as to the type of eye with which one is dealing. Iridectomy seldom produces a filtering scar, while iridencleisis will tend to produce such a drainage, should the eye clinically more like a "paroxysmal" type of vasomotor edema (angioneurotic edema). As knowledge develops, the appropriate treatments for the two conditions may come to differ substantially.

Also, if rapid simplex cases are separated from the acute glaucoma category, the latter becomes numerically an even rarer condition than it is thought to be at present—one in

TABLE 16

CLINICAL FINDINGS IN CHRONIC GLAUCOMAS

Symptoms Prodromal blurring and/or headaches possibly common to both	True Acute Congestive	Rapid Simplex
Simplex in opposite eye	Probably never	Fairly common
Chamber angle	Always narrow	Can occur with any type of angle
Pain, congestion, edema, etc.	Intense	Mild
Cupping of disc	Never present in first congestive attack. May appear in neglected cases	Fairly common (but some discs stand up for a long time)
Type of field loss	Concentric contraction, resembling optic atrophy	Of simplex type at any of its stages
Tension behavior	If attack subsides spontaneously or on treatment without operation, tension becomes low (abnormally) and remains so unless a further attack occurs. Confirmed by Sugar,[15] Duke-Elder[16]	Tension never to normal spontaneously. On miotics, reduction usually slight and rarely to normal (See Survey figures)
Postoperative behavior	Tension down to normal and remains so with temporary drainage only (iridectomy). If permanent drainage operation (iridencleisis) done, then cease to drain, but no further tension rise occurs	Functioning permanent type of drainage operation essential to normalize tension.

continue to require it, as rapid simplex cases undoubtedly do.

I think it is a point worth making, especially as it seems it may eventually be established that there is a difference in pathology between the two. Evidence has recently been produced (Robb-Smith and Lloyd [17]) that glaucoma simplex is a local manifestation of a general chronic vascular anomaly, and a number of my "rapid simplex" cases were included in this series.

True acute congestive glaucoma behaves

10 or more of all cases of glaucoma.

And finally it becomes impossible to speak of "acute attacks" in glaucoma simplex, though "congestive phases" may legitimately be said to occur in the terminal stages, especially of the "rapid" type.

Whatever the pros and cons of the foregoing, I feel that the detailed survey as a whole served to emphasize one main thing: That in our present state of knowledge, both clinical and scientific, it is not possible to make any effective subdivisions of the dis-

ease of glaucoma simplex. The most I have been able to attempt has been to bring under the same heading a fairly common type of case which has been previously considered alongside, and confused with, the much smaller group of true acute cases.

Simplex itself, however, shows all the signs at present of remaining one disease fundamentally, with individual variants probably produced by "patchy" distribution of the disease process as suggested by Duke-Elder (see below).

Let us therefore review briefly any pointers we can find in our own knowledge, and in the literature, to see whether we are, on this assumption, able to forecast the nature of the ultimate underlying causes. The factors at work, as far as our present knowledge goes, seem to be:

1. Excessive production of aqueous humor.

2. Relative failure of the resorption mechanism of the aqueous humor.

3. Damage to the region of the optic disc in the presence of raised or even normal ranges of intraocular pressure, namely, vulnerability of the disc.

Considering these factors one by one:

1. *Excess or abnormal production of aqueous.* This aspect is under intense and continuous fire from the fundamental researchers of the world. The precise mechanism of production of normal aqueous is not yet fully understood, though great efforts in this direction are being made in many laboratories, notably by Duke-Elder and his team at the London Institute, by Friedenwald, Kronfeld and others in the United States, and by many others.

Study of glaucoma simplex in experimental animals, however, is not possible as yet, because the disease cannot be produced experimentally. A strain of rabbits showing a condition of the eyes comparable to buphthalmos has been produced in Sweden and this may ultimately be of help in this direction.

Here, as so often elsewhere in glaucoma study, the point most significant to my mind is a negative one; that is, the work (Kronfeld[18] and Kronfeld, Lin, and Luo[19]) showing that significant changes in the amount of protein in the "primary" aqueous of the human eyes does not occur in cases of glaucoma simplex unless they enter a congestive phase, but do occur in all cases of glaucoma in this phase.

Recently, Robb-Smith and Lloyd[20] have produced evidence of vascular abnormality in monocular tissues of glaucoma patients, and this work, if confirmed, may establish the capillary factor (with which must be linked the formation of the aqueous) as a local specialized manifestation of a general vascular disease.

The parallel of epidemic dropsy tempts one to search for a toxic factor, possibly dietary. But the new field of histamine pathology, linked with the vegetative nervous system, may throw light here in the future. Also how far is Sugar's "A.C.P. reaction" an expression of this capillary factor?

2. *The available drainage rate.* This factor has received prolonged and thorough attention ever since the circulation of the aqueous, together with its egress at the anterior-chamber angle, was first postulated. It still seems probable that at least the major part of resorption of the aqueous takes place at the angle, though additional channels have been visualized via the iris and its crypts, the retina and choroid, and the optic nerve-head (Duke-Elder[21]), and via the outer third of the cornea (Ridley[22]), and even via the ciliary body.

Gonioscopic study of the chamber angle has produced a wealth of information of varying clinical value since its discovery by Trantas just before the turn of the century. It caused the change of classification in the United States from "shallow and deep chamber" to "narrow and wide angle" and has enabled the confirmation in vivo of the obstructive nature of certain of the rarer

glaucomas; for example, capsulo cuticulari, pigmentary glaucoma, aphakic glaucoma, and so forth.

It has been used to choose a site for operation (cyclodialysis), according to the various state of the angle in various sectors, and to study postoperative results. But it has not yet given us any fundamental revelations as to the nature of the drainage obstruction in ordinary wide-angle glaucoma.

The gonioscopic type of angle has been shown in my survey to bear little relation to the clinical behavior of simplex cases. In narrow angles mechanical interference with the trabeculum by the iris base can be easily envisaged, and I have actually observed this event in dilating the pupil in such eyes. It may well play an important part in the production of a true acute glaucoma, as the angle is always narrow in these cases. But in the simplex group, the angle may be of any type, and visible interference with the trabeculum is unusual, and then usually either a late manifestation or a postoperative phenomenon resulting from temporary emptiness of the anterior chamber.

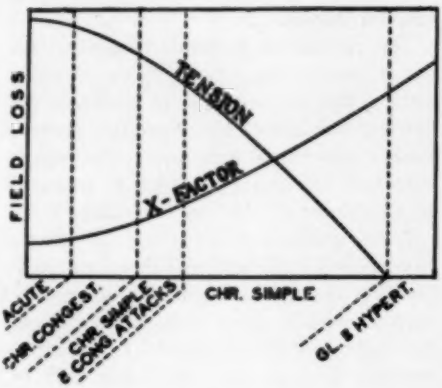

Fig. 2 (Lloyd). An attempt to express graphically the relation of tension to an unknown "X" factor in terms of damage to the disc (after Posner and Schlossman.[25])

I have little doubt that the canal of Schlemm mechanism is by no means the whole explanation of aqueous drainage, and consider this a promising field for future research. Duke-Elder[23] has forecast a "subtler obstruction to the drainage of the aqueous."

3. *Vulnerability of the optic disc* is no more than a means of expressing a mechanomorphic or purely hydraulic concept. This may not be entirely correct, as there is still some ground for conceiving the possibility of an excavating atrophy of the disc due to disease in its own tissues, and independent of intraocular pressure (Schnabel,[24] and many others). However this may transpire, it should be remembered that Posner and Schlossman[25] attempted to express graphically the relation of tension and what they regard as an unknown "X" factor in terms of damage to the disc (fig. 2).

It is tempting to think that the "X" factor consists entirely or almost entirely in vulnerability of the disc. Mathematical looking formulas are never popular in ophthalmology, and are not always understood, but could not the situation in simplex be covered, or nearly so, by the formulas:

$$(1)\quad \frac{\text{Aqueous production}}{\text{Available drainage rate}} = \text{Tension}$$

(2) Raised tension × Time in existence × Disc vulnerability = Damage at disc

Summary

1. The historical background of attempts to subdivide the disease entity, glaucoma simplex, is briefly reviewed and an attempt made to assess the measure of success.

2. The objects of the survey are set forth as an attempt to study certain dubious points in accepted teaching and classification, to see whether any such subdivision is possible on the observed detailed clinical behavior of the series of cases, and to search for any indications of the underlying causes of the disease.

3. The detailed clinical behavior of 249 "reputable" cases of glaucoma simplex with

and without complications is set out in the form of a statistical survey.

4. Methods and results of treatment are set out in detail together with complications, their relative frequency, and their consequences.

5. A clinical type of the disease provisionally called "rapid simplex" is defined both from the survey and theoretically, and its confusion with true acute glaucoma explained.

6. The survey seems to support the view that glaucoma simplex cannot be subdivided on clinical observation, even in the detail given, and that it is probably a single disease entity with individual variations in behavior, possible reasons for this being discussed.

7. Our present knowledge of the disease is reviewed in this light and possible avenues of approach to the underlying causes indicated.

The Eye Hospital,
Walton Street.

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FURMETHIDE IODIDE IN THE PRODUCTION OF DACRYOSTENOSIS*

ROBERT N. SHAFFER, M.D., AND WILLIAM L. RIDGWAY, M.D.
San Francisco, California

It is the object of this paper to warn ophthalmologists against the prolonged use of furmethide in the treatment of glaucoma. Permanent obstruction of the tear passages has been observed in a large percentage of cases in which the drug was used for more than three months.

Furmethide (Furtrethonium iodide, Smith, Kline and French) is a recent addition to drugs for treating glaucoma. In 1940, the animal pharmacology was developed by Fellows and Livingston.[1] Myerson and Thau[2] studied its ocular effects and thought it safe and worthy of a trial as a miotic. In 1943, the use of furmethide in comparison with other miotics for the treatment of glaucoma was described by Uhler.[3] Further studies were contributed by Ella Uhler Owens and A. C. Woods in 1946.[4]

In none of these papers was any evidence noted of local sensitivity or irritation to the drug. The only untoward reaction in over 100 cases was one patient who developed severe perspiration, salivation, and lacrimation.[3] In 1949, Scheie stated that allergy to furmethide could occur and that tearing was a more prominent symptom than itching.[5]

For five years we have been using 10-percent furmethide sporadically in the treatment of glaucoma. The drug was used only in those cases which were not well controlled by the more common miotics. Its ability to control tension seemed somewhat better than two-percent pilocarpine solution; consequently it has been used increasingly over the past two years.

During that time there has been a corresponding increase in the number of patients asking for relief from their tears. A thorough investigation of patients, from our private practices and from the Glaucoma Clinic of the University of California, confirmed our opinion that any furmethide user is in grave danger of developing dacryostenosis.

Lacrimation is the first symptom of early toxicity, and it usually starts in from three to six months after the beginning of treatment. At this stage the tear ducts can be irrigated successfully. If furmethide is not discontinued, actual mechanical block will occur within another three to six months.

The obstruction can occur anywhere in the tear passages and is usually multiple. The commonest and most annoying stoppage is at the common punctum. In passing a No. 2 Bowman's probe along the canaliculi, definite adhesions are encountered which can be broken in the early stages.

In two cases a membrane could be seen sealing the opening of the punctum. When this was broken with a punctum dilator, bleeding occurred. Two patients had occlusions midway in the tear sac, and one of these suffered a dacryocystitis following probing. The major pathologic change, however, seems to be in the canaliculi.

Conjunctival scrapings were made from several typical cases and stained with Giemsa stain. These showed consistent findings of nonspecific chronic inflammation. There were no eosinophils, no keratinization, and no bacteria. There were occasional polymorphonuclear leukocytes, monocytes, and lymphocytes.

Biopsies were also taken in several cases. The conjunctivas showed nonspecific acute and chronic inflammation. There was moderate desquamation with edema of the epithelium and with scattered mononuclear cells in the edema spaces. The substantia propria showed diffuse chronic inflammation with mononuclear and polymorphonuclear cells in the area immediately adjacent to the basal cell layer of the epithelium. No eosinophils were seen. The deeper conjunctival layers

* From the Division of Ophthalmology, University of California Medical School.

showed no alteration from normal. It was felt that there was no hyperkeratosis or alteration of the growth pattern of the conjunctival epithelium.

The photomicrographs (figs. 1, 2, and 3) are of sections through the palpebral conjunctiva and the punctum. The lumen of the punctum shows the typical fibrous occlusion with no marked changes in the epithelium. Some of the sections showed keratinization of the superficial layers of the epithelium with evidence of hyperplasia and folding. There was also some downgrowth of the

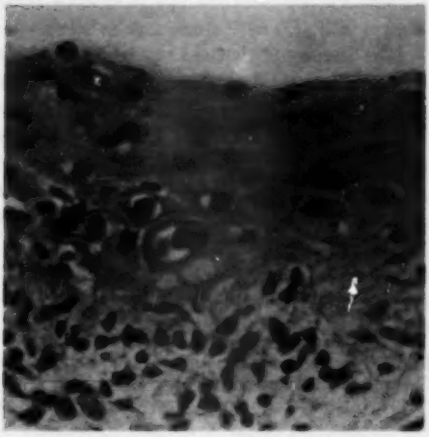

Fig. 1 (Shaffer and Ridgway). Biopsy of inferior palpebral conjunctiva, showing nonspecific inflammation with epithelial edema.

interpapillary pegs, but no actual malignant transformation.

The number of patients available for this study has been relatively few. In most cases, furmethide was used for only a few days if the elevated tension was not promptly brought under control. Many patients were on furmethide for one to eight weeks, but no epiphora appeared in anyone who used it for less than three months. Only two patients had tearing in three months' time, but one of these had already developed a small adhesion in the middle of the lower canaliculus of one eye. The other eye was watery, but the tear passages were patent.

Fig. 2 (Shaffer and Ridgway). A section of the punctum near the surface, showing partial occlusion of the lumen by granulation tissue.

In only 21 patients was furmethide used for more than three months. However, as can be seen by referring to the statistical summary, 71 percent of these patients developed tearing. Most of the actual obstructions seemed to appear between six and 12 months after furmethide was started. All patients with tearing, but with patent ducts, later developed dacryostenosis if furmethide therapy was continued. Of the entire group, only one patient was on furmethide more than 12 months without developing tearing.

One-hundred-seventy glaucoma patients were selected at random as a control group. These patients had been treated over a number of years with pilocarpine, eserine, pro-

Fig. 3 (Shaffer and Ridgway). A deeper section of the punctum, showing almost complete fibrous occlusion of the lumen.

stigmin, floropryl, or carcholin. Four patients, or only 2.5 percent of this group, complained of tearing. All of these had been on pilocarpine. Two of them had actual obstruction of the ducts. We are convinced that this significant statistical difference is entirely due to furmethide.

The only other possible reason for these results is that either the buffer or the preservative is at fault. The pH of furmethide is adjusted to approximately 7.4 and it is buffered with sodium phosphate which is commonly used in eye solutions. The preservative is sodium ethyl mercuri thiosalicylate, 1:100,000. This preservative is also used in several other Smith, Kline, and French specialties and apparently no deleterious effects have ever been noted.

TABLE 1
STATISTICAL SUMMARY

A	
21 patients using furmethide for three months or longer:	
15 had tearing within 3 to 12 months.....	71%
B	
15 patients with tearing:	
12 had demonstrable occlusion of tear passages.....	80%
C	
Control Group	
170 glaucoma patients using other miotics:	
4 had tearing.....	2.5%

SUMMARY AND CONCLUSIONS

Seventy-one percent of glaucoma patients treated by furmethide for more than three months developed permanent occlusions of the canaliculi and tear ducts. In a large control series, only 2.5 percent of the patients treated by standard miotics developed tearing.

It is suggested that the use of furmethide be restricted to short-term therapy, such as in the presurgical reduction of tension, or as a rest period from other miotics. If it seems advisable to continue furmethide for more than two months, the patient should be warned to report to the physician at once should tearing develop.

490 Post Street (2).

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THE PROBLEM OF TORTUOSITAS VASORUM RETINAE*

PAUL WEINSTEIN, M.D.
Budapest, Hungary

Whether tortuositas vasorum retinae should be regarded as a pathologic or congenital condition has been the subject of some debate. Take, for example, Guist's phenomenon occurring in hypertonia and consisting of corkscrewlike meanderings of the venules surrounding the macula.

Guist believes this pattern to be a proof of essential hypertonia, while von Sallmann is of the opinion that it is a circulatory deficiency developing because of a congenitally reduced vascularity. In this paper, it is my intention to deal only with retinal vascular sinuosity which is congenital in origin.

Gauss[1] has published statistics which show that, out of 150 cases chosen at random, 44 (30 percent) showed tortuous sinuosity without any apparent cause. Thoma[2] investigated the elasticity of retinal arteries and emphasized that decreased elasticity of the vascular walls is the cause of the increased meandering of the vessels of the eyeground and should be regarded as the earliest symptom of arteriosclerosis.

Plesch[3] believes the sinuosity of the temporal artery to be characteristic of arteriosclerosis. He does not emphasize hardening of the vessel but rather points to softening and weakening of the vessel wall.

A sinuous temporal artery is only a partial sign of a general decreased tonicity. Reduced tonicity of the longitudinal muscle fibers causes the elongation and, thereby, the sinuosity of the vessel. Decrease in tonicity of the circular muscle fibers results in dilatation and is responsible for the voluminous pulse. Sinuosity of the vessels is, therefore, the result of decrease in both tonicity and elasticity of the vascular system.

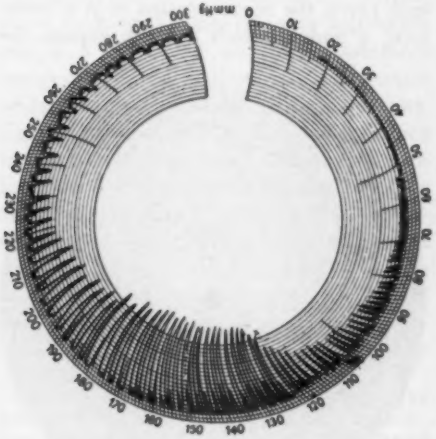

Fig. 1 (Weinstein). Prearteriosclerotic oscillogram.

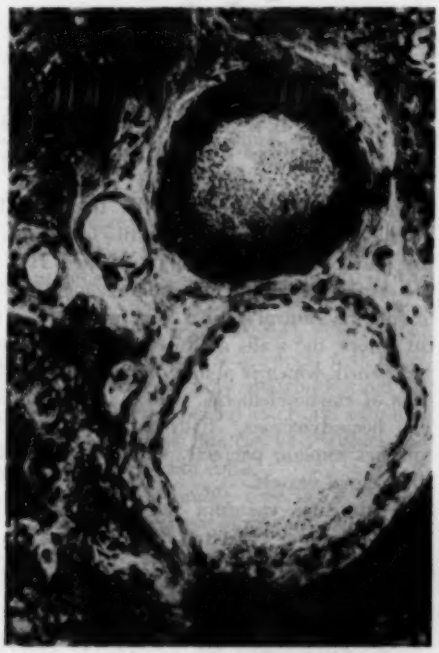

Fig. 2 (Weinstein). Histologic picture of the central retinal vessels in a case of prearteriosclerosis.

* From the Department of Ophthalmology, Hospital of the Jewish Community.

In oscillographic investigations of this condition, the oscillograms showed great amplitudes in cases of hemorrhage of the eyeground (fig. 1), a peculiarity which I have termed "the hemorrhagic curve," and

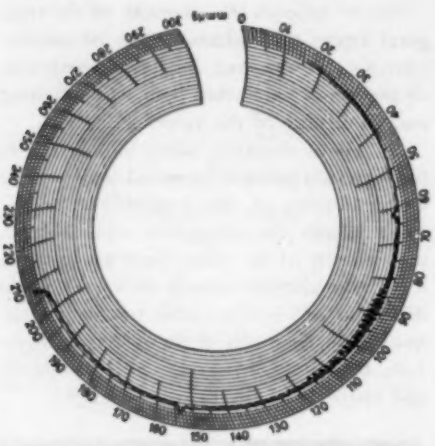

Fig. 3 (Weinstein). Hypoplastic oscillogram.

which signifies, according to Plesch, prearteriosclerosis. It is loss of elasticity of the circular muscle fibers that produces the wide oscillations.

Histologic study (fig. 2) of the central retinal artery in such cases disclosed that the media were considerably thickened. Hyalin degeneration was present. In some of the cases, the central retinal vein was normal; in others, the walls of the vein had become thickened, which is a sign of hardening and loss of elastic elements. Guist's experiments in hemodynamics, hydromechanics, and physics explain perfectly such sinuosity of the retinal vessels.

Tortuositas vasorum retinae was found as an accessory symptom in 12 of my cases. Pseudopapillitis was concurrently present in three cases. My cases also confirmed Gauss's observation that the blood pressure was always conspicuously low (100/70 to 140/70 mm. Hg).

The ages of the patients varied between 20 and 61 years. In some of the cases, spontaneous venous pulsation showed beyond the papilla. Ocular tension was within the lower limits of normal (12 to 20 mm. Hg (Schiøtz).

Most perplexing was the tonoscillogram which, in every case, showed the so-called hypoplastic curve (fig. 3). In some cases, almost no oscillation was perceptible, although there was no possible presence of endarteritis. Circulation was always normal. This would seem to be a verification of the observation that, in cases of sinuosity, the tonicity of the vascular system (asthenic hypoplastic system) is generally decreased. The elasticity of the longitudinal muscle fibers is probably reduced while, at the same time, the elasticity of the circular fibers is preserved. The pulse volume is reduced.

Under normal conditions, the cardial pulse wave proceeds toward the eye and produces a plethismographic oscillation synchronous to the cardial revolutions—a coincidence which I have been able to register by means of the von Recklinghausen grypotonograph (fig. 4). Usually, this curve is identical to the brachially registered sphygmogram. In such cases, the ocular tension is at a lower level, a finding which helps to explain the

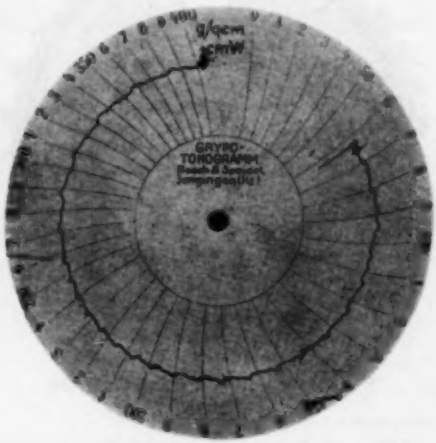

Fig. 4 (Weinstein). Sphygmogram of the eye.

decreased ocular tension in cases of sinuosity of the retinal vessels.

When reduced elasticity and tonicity of the vessel walls are associated with congenital hypermetropia, meandering of the retinal vessels is more likely to occur because, in the less-extended space of the hypermetropic globe, tortuositas vasorum retinae develops more easily.

SUMMARY

My investigations would seem to indicate that congenital factors controlling the tonicity and elasticity of the general vascular system are of considerable significance in the mechanism of tortuositas vasorum retinae. Further corroboration is provided by the hypoplastic character of the oscillogram, the low blood pressure and ocular tension, and the frequently visible extrapapillary venous pulsation.

V. Szemelynok-u. 9-11.½ 3.

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OPHTHALMIC USE OF TERRAMYCIN*

ARNO E. TOWN, M.D.
Philadelphia, Pennsylvania

In January, 1950, our armament of drugs was enhanced by the addition of a new, broad-spectrum antibiotic known as terramycin.† It is produced from a species of earth-mold (Streptomyces rimosus) different from those forming the base of other antibiotics, and is a crystalline amphoteric substance which can be reacted chemically with certain acids or bases to form stable, crystalline salts. Crystalline terramycin hydrochloride, which is bright yellow in color, is the salt which has been made available in capsule form for oral administration. It is highly stable, maintaining its potency for a period of 12 months when stored at room temperature, and is more readily absorbed than the amphoteric form.

Studies to date at the Mayo Clinic[1] and elsewhere indicate that terramycin is one of the most versatile antibiotics, possessing a wide range of potent antimicrobial activity, and that some strains of organisms are more sensitive to terramycin than to other antibiotics. It is effective in vitro and in vivo against a variety of micro-organisms, including many of the Gram-positive and Gram-negative bacteria, both aerobic and anaerobic, the Rickettsia, and certain of the viruses.

Terramycin is well tolerated, even by patients who experience side effects with other antibiotics. Occasionally gastrointestinal irritation has been reported after oral administration, but usually this can be overcome by giving the drug with milk.

Because of favorable reports on the investigations of the use of terramycin in general disease conditions, we asked the manufacturer to make available a suitable ophthalmic solution for local instillation. This was prepared by adding distilled water to buffered crystalline terramycin hydrochloride in proportions to give a 0.5 percent solution

* From the Department of Ophthalmology, The Jefferson Medical College of Philadelphia. Read before the Section on Surgery at the 100th annual session of the Medical Society of the State of Pennsylvania, Philadelphia, October, 1950.

† Terramycin for this investigation has been supplied by Chas. Pfizer Co., Inc., Brooklyn, New York.

having a pH index of 8.2. The ophthalmic preparation is stable as submitted in powder from, but unstable when maintained in aqueous solution longer than 48 hours. It should be kept under refrigeration when not in use.

The aqueous solution proved to be less "wetting" than water alone, and tendency for the lids to repel the solution was noted. While this fault does not have an adverse effect on the action of the terramycin, it does contribute to a waste of the drug and is a nuisance to the patient. We, therefore, are trying methyl cellulose‡ as the diluent, and find it to have better adhesive qualities. In addition, preliminary tests indicate that it possesses a higher degree of stability than does the aqueous solution. The action of the terramycin is equally effective in either solution.

An ophthalmic ointment also is now available, and this should prove to be valuable in the treatment of blepharitis since lid margins are never properly wetted with solutions.

In our investigation, ophthalmic terramycin solution has been used in 132 ocular infections, locally administered at frequent intervals (every two hours or more often) over a short period of time. When the infectious process was associated with general disease or when the deeper structures of the eye were involved, the local application of terramycin was fortified by capsules orally.

The drug is relatively nontoxic, as demonstrated by the size of the oral dose, usually at levels of two to five gm. per day. In no case was terramycin found to be any more irritative to the conjunctiva than other solutions routinely employed in practice, and only one case of sensitivity to the drug has been observed—in contrast to sensitivity reaction so often encountered in the administration of penicillin.

Our experience in ocular infections bears out the findings of pioneer investigators of terramycin, that the antibiotic has a high degree of potency and a wide spectrum of activity. Our own investigations and those of others in the field of general disease indicate that it should be effectual in pneumococcal, streptococcic, staphylococcic, gonococcal, luetic, and Brucella ocular infections. Furthermore, since it has been found to be effective in cases of herpes zoster, it should be a valuable aid in the treatment of some corneal ulcers due to a virus.

The use of terramycin in our 132 cases proved effective in 114, and of no value in 18. The ocular infections treated may be broken down into the following classifications.

Staphylococcic infections

Terramycin was used to treat 48 patients with conjunctivitis produced by staphylococci, aureus and/or albus, either alone or with other organisms. In some of these cases there was an associated blepharitis and/or keratitis. In most instances the infection was cleared in from 24 to 48 hours, although a few of the more obstinate cases persisted from one to four weeks. A few recurred when drops were stopped, but were later cleared when therapy with terramycin was resumed.

Relief of such symptoms as burning and itching was noted almost immediately, even before objective improvement was seen. In the treatment of conjunctivoblepharitis, no other technique was employed, such as the removal of scales and crusts and the application of silver nitrate. In many instances previous therapy had been ineffectual.

In only two cases was the drug totally ineffective in treating a staphylococcic infection—in one, nonhemolytic streptococci also were isolated; in the other, there was an associated punctate keratitis. One patient with keratoconjunctivitis sicca in which the culture shows Staphylococcus aureus, with the clinical appearance of an old, mild trachoma, was symptom-free for a period of one month as long as she used terramycin; however,

‡ The methyl cellulose was supplied by the Iso-Sol Company, Brooklyn, New York.

after that time the drug was no longer effective.

One case of staphylococcic conjunctivitis reported by Dr. Rychener[2] was associated with severe impetiginous lesions of the nares and upper lip. Terramycin drops in the eye every two hours and 250 mg. by mouth every six hours produced a cure within three days, which he describes as "miraculous." Dr. Grove[3] reported a case of severe blepharitis associated with an equally severe seborrheic condition of scalp, neck, brows, and so forth. This patient had been under treatment by him for a long period of time, and exceedingly better results were obtained with terramycin than with anything previously used. This experience was repeated in many of the chronic conditions which were treated with terramycin.

Eight cases of infected chalazia were treated. Three in early stages cleared spontaneously within three to five days. The remaining five chalazia were excised without complication when inflammation subsided.

Pneumococcal conjunctivitis

Seven patients with pneumococcal conjunctivitis were treated. The terramycin was used every two hours for two to four days, after which time the patient in each case was free of symptoms. One recurrence was noted after one week, but the condition was cleared after an additional 10 days of terramycin therapy.

Keratitis and virus infections

Fifteen cases of superficial punctate keratitis and marginal corneal ulcers were treated. Four obtained prompt relief with the use of terramycin, but as soon as the drug was stopped there were recurrences; in one of these cases aureomycin had been used previously, and the effect of the two drugs was the same. There was no response to terramycin in seven cases, while one with an associated allergy was essentially clear in one month. One after two months shows marked improvement, though there is still an occassional punctate area to be seen. One was completely cleared in two days, one in nine days.

One case of filamentary keratitis was clear in two days with the use of terramycin solution fortified by oral administration of the drug.

One case of dendritic ulcer responded quickly to the drug, and the cornea was clear in two days.

Two cases of bacillus proteus corneal ulcers were treated every hour for 72 hours and 96 hours respectively, with no appreciable effect.

In one case of severe herpes simplex there was no response to terramycin used every two hours over a period of 96 hours, but in another with keratitis in herpes zoster the patient experienced immediate relief.

Two cases, diagnosed as Parinaud's oculoglandular syndrome and thought to be of virus origin, were treated. One was completely cured in two weeks, while there was no effect on the progress of the disease in the second.

Streptococcic infections

Only four cases in which this organism was isolated were treated with terramycin. In two, the condition cleared within three days. In the third case, culture prior to cataract extraction showed the presence of streptococci. Culture one week later was negative. We now use terramycin routinely as a prophylaxis preoperatively.

In the fourth case, which has been included also under the classification of staphylococcic infections, both staphylococci and streptococci were isolated. Terramycin here proved ineffectual.

Follicular conjunctivitis

There were six patients with acute follicular conjunctivitis of unknown eitology in whom it was impossible to isolate a microorganism. All of the patients responded well to the antibiotic within 48 hours, although some may have recovered spontaneously.

Morax-Axenfeld conjunctivitis

Six patients with conjunctivitis in whom the diplobacillus of Morax-Axenfeld was isolated were treated with terramycin. Relief from symptoms was obtained in from two to four days.

Koch-Weeks conjunctivitis

Six cases of conjunctivitis in which smears showed the Koch-Weeks bacillus were treated. All cleared in from one to three days. It is well known that the Koch-Weeks type of conjunctivitis clears spontaneously, but it is felt that the use of terramycin shortened the course of the infection.

Dacryocystitis

Three cases of chronic dacryocystitis, including one congenital, were treated with terramycin. In each case the infection in the sac was cleared within one week. No recurrences have been noted.

Infections following trauma

Five patients with infection secondary to trauma received treatment with terramycin. In all the infection cleared within three days without complication. In one case reported by Dr. Shepherd,[2] a corneal ulcer developed after the removal of a foreign body. Sulfacetimide, atropine, and bacitracin first were used without improvement. Two days later the ulcer had increased and there was a flare in the anterior chamber. Terramycin was started and instilled every 15 minutes. Nine hours later the reaction had subsided and the eye was quiet. In two days the ulcer had healed.

Trachoma

In one suspected case of trachoma with pannus and keratitis, terramycin was used for three weeks. Subjective improvement occurred in three days, and clinical improvement was present when the patient was seen on the eighth day. The use of terramycin should be investigated in localities where trachoma is endemic.

Unclassified

The offending organisms were not isolated in a group of 16 conjunctival infections. Terramycin was administered in each case. In 12 the infection cleared in from one day to one week; in four the therapy was ineffective. Although, from the scientific standpoint, these figures add no weight to the investigation, it is our belief that they do emphasize reasonably the wide range of activity possessed by the drug.

Summary

Terramycin in 0.5 percent alkaline solution has been found to be nonirritating to the conjunctival tissues and in a series of 132 cases caused but one instance of drug reaction. An acid solution of terramycin in methyl cellulose is equally effective, has better adhesive quality, and possesses greater stability. An ointment is now available which should prove to be valuable in the treatment of blepharitis.

In a series of 132 cases, terramycin proved to be a potent agent against most of the micro-organisms and some of the viruses which cause external ocular infections. Results in the treatment of those attributable to viral diseases have not been as positive as in most other infections treated with terramycin, but they are sufficiently favorable to warrant further investigation. The effect of terramycin in trachoma should be studied.

Terramycin may be highly effective even when other antibiotics fail, and may be well tolerated when other antibiotics are not.

1025 Walnut Street.

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UNILATERAL THYROTROPIC EXOPHTHALMOS*

E. Howard Bedrossian, M.D.
Drexel Hill, Pennsylvania

The purpose of this presentation is to emphasize the difficulty one may encounter in arriving at an early diagnosis of unilateral exophthalmos, especially when the underlying pathologic condition is of endocrine origin, and to review the present-day concept of the mechanism producing exophthalmos of endocrine origin. Although unilateral cases usually become bilateral and are then more quickly diagnosed, we should be constantly on the alert for such a situation, so that valuable time will not be lost before starting treatment, and the patient's eye jeopardized in the meantime.

There are two groups of cases which present different clinical features but which, some investigators feel, have a single etiologic basis; other authors, however, feel that the underlying cause is different. These cases occur in individuals with both hyper- and hypothyroidism, with extremes ranging from severe thyrotoxicosis to marked myxedema. This latter group of cases with exophthalmos has a variety of synonymous names used to describe it—malignant exophthalmos, progressive exophthalmos, exophthalmic ophthalmoplegia, postoperative progressive exophthalmos, special ophthalmopathic type of Graves's disease, and, finally, thyrotropic exophthalmos.

Means and Mann believe that the exophthalmos does not differ in type but only in course and degree. It seems likely that the pituitary produces the substance causing exophthalmos, while the thyroid produces the substance controlling it (fig. 1-a). Exophthalmos results from production of excessive amounts of the thyroid-stimulating hormone by the pituitary, perhaps initiated by nervous stimulation through the hypothalamus.

This excess thyroid-stimulating hormone causes exophthalmos and also causes the normal thyroid to respond with hypertrophy and excessive secretion of thyroid hormone. The excessive thyroid hormone, besides stimulating metabolism, acts as an inhibiting mechanism of the pituitary, causing lessened production of thyrotropic hormone. Thus, exophthalmos does not become excessive because the thyrotropic hormone, although produced in greater amounts, is controlled by a regulatory mechanism (fig. 1-b).

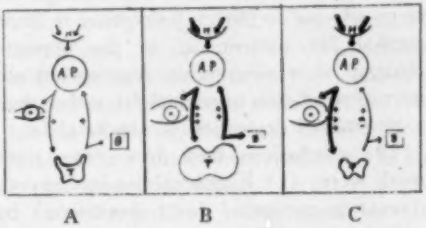

Fig. 1 (Bedrossian). The pituitary-thyroid axis. (After Means). (a) Normal. (b) Thyrotoxic. (c) Thyrotropic.

In the case of progressive exophthalmos, the excess amount of thyrotropic hormone is produced as before, but instead of stimulating normal thyroid tissue, the thyroid for some unknown reason seems unable to respond with the production of greater amounts of thyroid hormone. Thus, the pituitary goes on secreting more of its thyrotropic hormone and the exophthalmos increases (fig. 1-c).

Obviously, there are a number of suppositions in this theory and just where the abnormality occurs in this usually self-regulatory mechanism is not definitely known.

Mulvany, on the other hand, believes that

* From the service of Dr. Edmund B. Spaeth, chief, Department of Ophthalmology, Graduate Hospital of the University of Pennsylvania. Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, December, 1949.

the exophthalmos is due to an increase in orbital contents. He describes different microscopic findings in the two varieties of exophthalmos. In cases of thyrotoxic exophthalmos, he finds widespread neuromuscular degeneration, occasional infiltration of round cells, fat infiltration, and some fibrous replacement in the disintegrating muscle and nerve cells. In malignant exophthalmos, he finds enlargement of the muscles, fibrosis which is often widespread through the muscles, edema, degeneration, and round-cell infiltration.

On the thyrotoxic side, these views of Mulvany seem to be substantiated by the work of Rundle and Pochin, who analyzed the orbital contents in 17 cases of thyrotoxicosis postmortem and compared them with controls. They found the different muscles were affected in direct proportion to their normal fat content, as in the opposite changes of wasting. This suggests an abnormal regulation of normal fat, rather than a generalized deposition of abnormal fat.

The conclusions they drew from their work were: (1) Exophthalmos in Graves's disease in accounted for quantitatively by an increase in bulk of the retrobulbar tissues. (2) The increase is relatively greatest in the eye muscles of which the average fat content is doubled. The changes are most marked in the levator muscle, which is known to be responsible for lid retraction. (3) The increase in muscle fat may be extensive before the residual tissue fat is sufficiently increased to cause exophthalmos. (4) Fat changes similar to those in patients with exophthalmos were present in cases of thyrotoxicosis without exophthalmos, although the changes were to a lesser degree.

It therefore apears that thyrotoxic exophthalmos merely results from a high degree of a process common to all cases of thyrotoxicosis.

On the thyroptropic side, most pathologic specimens of eye muscles have been made on postthyroidectomy cases developing exophthalmic ophthalmoplegia. Burch described the muscles as enlarged and showing degeneration, edema, and infiltration with lymphocytes.

Naffziger and Jones reported four cases in which the ocular muscles were three to eight times larger than normal and contained edema and round-cell infiltration, often in perivascular form. They also showed loss of muscle architecture, increase in fibrous tissue with areas of hyalinization, fragmentation, and destruction of muscle fibers.

Stallard reported a case of ophthalmoplegia, not following thyroidectomy, in which there was interstitial fibrosis and chronic inflammatory round-cell infiltration, but no definite degenerative changes of muscle fibers.

Experimental production of exophthalmos in animals by the injection of pituitary extract has been well established since the first studies of Schockaert in 1931. Smelser has shown that injecting anterior pituitary extract into thyroidectomized guinea pigs produces hypertrophy of orbital fat due to increased water content, and not fat content. Other fat tissues in the body were similarly affected but to a lesser degree.

Pochin also has shown that the exophthalmos produced by anterior pituitary injections is quantitatively accounted for by edema of the orbital tissues, particularly affecting the dorsal lacrimal gland and its sheath. He also showed that thyroidectomy made no difference in the amount of exophthalmos.

Recent studies by Jefferies indicate that the degree of exophthalmos and fat deposition in the liver is not changed by comparable doses of pituitary extract in the intact versus thyroidectomized guinea pigs. His work also indicates that there is a separate exophthalmic and fat-mobilizing principle associated with the thyrotropic hormone in pituitary extracts, since the thyrotropic factor can be inactivated while the other two principles remain active.

From these observations, it would seem that the mechanism producing exophthalmos

from primary hyperthyroidism is different from that caused by excess thyrotropic hormone, and that one should try to classify the case as to the underlying pathologic condition in order to treat the patient properly. This often is difficult since a secondary hyperthyroidism may be present as the result of excess thyrotropic hormone and many cases will then fall somewhere in between the two extremes.

Table 1 summarizes the essential clinical and pathologic differences between the thyrotoxic and thyrotropic types of exophthalmos.

Treatment seems to be more effective when either primary hyperthyroidism or hypothyroidism is present, since thyroidectomy can be performed on the one hand and thyroid extract given on the other hand. In some progressive cases, X-ray therapy to the pituitary and thyroid has been tried, and hormones, such as stilbesterol, have been given, but neither treatment has been very successful. A tarsorrhaphy and Krönlein, or Naffziger, decompression of the orbit are often necessary to prevent the complicating exposure keratitis and panophthalmitis which may result.

The following case report illustrates some of the problems frequently encountered in thyrotropic exophthalmos, especially when it presents itself with unilateral symptoms.

Case report

Mr. R. C., a-45-year-old white man, a tailor by trade, was first admitted to the Graduate Hospital on October 18, 1948, because of a painful and bulging right eye. He had had intermittent diplopia in 1937 and 1942, at which times he was examined and found to have diabetes for which he was treated and the diplopia disappeared.

In 1947, the diplopia reappeared and was annoying enough to require him to wear a frosted lens over his left eye. He wore this for eight months when he developed exophthalmos, impaired ocular movements, and a corneal ulcer in the right eye. X-ray films taken at that time were reported as showing a tumor in his right orbit. For this, he was given X-ray therapy, following which the exophthalmos receded, and so did his hairline. Within the next two months, the exophthalmos and corneal ulcer reappeared and he was admitted for the first time to the Graduate Hospital.

The patient was a known diabetic, mild enough to be controlled on diet alone. His mother had had diabetes and cancer and died at 58 years of age. His father had had renal disease and died at the age of 47 years.

Physical examination showed alopecia, a systolic heart murmur over the apex, and blood pressure of 145/85 mm. Hg; pulse, 80; height, five feet-four inches; weight, 140 pounds.

Ophthalmic examination. Vision was: O.D., 6/60; O.S., 6/12. There was exophthalmos, chemosis, corneal anesthesia, and ulcer of the right eye, with impaired vertical and left lateral rotation, O.D. The fundus of the right eye was not visualized. External and fundus examination of the left eye gave normal findings.

Laboratory. Blood count, urinalysis, and X-ray studies of the orbit were all normal. No tumor was visualized.

Course. On October 22, 1948, an orbitotomy and biopsy were performed. The specimen was reported as chronic adenitis of lacrimal gland and surrounding tissue. The patient was discharged on medical treatment to protect the cornea.

Second admission. On January 16, 1949, the patient was readmitted because his vision had now dropped to counting fingers and the right eye was extremely painful. Vision of the left eye was still 6/12, correctible to 6/6. The right eye was fixed, chemotic, and protruding; left eye, normal. Blood, urine, and X-ray studies were again normal. No pathologic condition of bones or optic foramen was reported.

Course. On January 18, 1949, the right eye was enucleated. The biopsy of the retro-orbital mass was reported as: "This is not a

TABLE 1

COMPARISON OF THE CLINICAL AND PATHOLOGIC DIFFERENCES BETWEEN THYROTOXIC AND THYROTROPIC EXOPHTHALMOS

THYROTOXIC	THYROTROPIC
CLINICAL	CLINICAL
1. OCCURRENCE: Early adult—females predominantly.	1. OCCURRENCE. Middle-age—males predominantly.
2. HYPERTHYROIDISM	2. NORMAL OR HYPOTHYROIDISM
A. *Signs and symptoms*	A. *Signs and symptoms*
1. Increased susceptibility to adrenalin a. Accelerated pulse b. Increased circulation rate c. High systolic pressure, wide pulse pressure	1. Apathy, lethargy, slow cerebration
2. Nervous excitability	2. Dry, sparse, brittle hair
3. Muscular weakness and fine involuntary tremor	3. Increase body fat and hypercholesterolemia
4. Increased B.M.R. (skin hot and moist, intolerance to heat, tolerance to cold)	4. Decreased B.M.R. (skin cool and dry, tolerance to heat, intolerance to cold)
5. Dissipation of fat stores, wasting	5. Thick, puffy skin (due to albuminous substance of over 13% protein)
6. Increased nitrogen and calcium excretion	6. Cardiac dilitation
7. Disturbance of CHO metabolism (hyperglycemia glycosuria, decreased sugar tolerance, etc.)	
8. Enlarged thymus in 80%	
9. Susceptability to O_2 deficiency	
B. *Laboratory*	B. *Laboratory*
1. Blood iodine, 30μg% (Normal is 10–12 mostly organic form)	1. Blood iodine, 7–9 μg.%
2. Inactive thyrotropin excreted in urine	2. Inactive plus active thyrotropin excreted in urine
3. Increased creatinuria	
3. EXOPHTHALMOS	3. EXOPHTHALMOS
A. *Not marked*, usually bilateral and equal (average protrusion 2.5 mm. when Norm. taken at 12.5)	A. *More marked*, may be unilateral; if bilateral, often asymmetrical
B. *Classical signs* (May be present without exophthalmos) 1. Parry's sign—exophthalmos 2. Dalrymple's sign—widening of palpebral fissure due to lid retraction 3. von Graefe's Sign—upper lid lags when eye looks down 4. Kocher's sign—globe lag (reverse von Graefe's) 5. Stellwag's sign—infrequent blinking 6. Moebius's sign—convergence weakness 7. Gifford's sign—difficulty in everting upper lid 8. Joffroy's sign—absence of wrinkling of forehead when patient looks up, with lowered head 9. Rosenbach's sign—tremor of lids when effort made to close them gently 10. Jellineck's sign—pigmentation of outer surface of closed lids 11. Suker's sign—visual fixation from extreme lateral rotation 12. Wilder's sign—jerking or twitching of globe when moving eye from extreme abduction to adduction	B. *Classical signs* (may or may not be present; when present due to exophthalmos)
C. *Little or no ophthalmoplegia* (May have associated toxic myasthenia with ptosis of levator and involved orbicularis)	C. *Ophthalmoplegia* (usually present) 1. Levator and orbicularis spared 2. If unilateral, always on more protruding side 3. In plane and not individual muscle a. Elevation affected most if unilateral b. Lateral rotation affected most if bilateral 4. Proportional to degree of exophthalmos (most likely due to rise in pressure within muscle cone from edema and cellular infiltration.
D. *Little resistance to pressure*	D. *Marked resistance* to pressure
E. *No edema* (May have bulging or protrusion of lids from orbital overfilling, due to prolapsing orbital fat	E. *Edema* of lids and conjunctiva characterized by dependency and pitting
PATHOLOGY	PATHOLOGY
General wasting of muscle fibers with loss of striation, fibrillation, and amorphous granulation of the sarcoplasm. Muscles normal in size. No edema or roundcell infiltration but increase in amount of muscle and orbital fat.	Muscles much larger than normal. Interstitial fibrosis, edema, and chronic inflammatory lymphocytic infiltration often in perivascular form.

neoplasm. It is a mixture of tissue such as nerve fibers, striated muscle, fibrous tissue, and a few scattered plasma cells and lymphocytes. Considerable edema is present. Diagnosis: Inflammatory process." The patient was discharged on January 30, 1949.

Third admission. On October 4, 1949, the patient was readmitted because the left eye had become swollen and movement impaired.

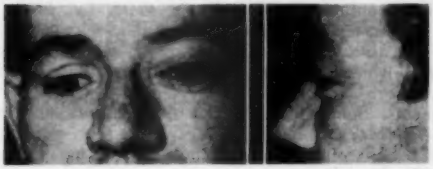

Fig. 2 (Bedrossian). Front and lateral view of patient's left eye showing exophthalmos and dependent edema of lower bulbar conjunctiva.

His vision was still correctible to 6/6, but his ocular rotations were impaired in all directions of gaze. There was a slight exophthalmos present. Field of vision and fundus examinations were normal.

Laboratory. Blood count, urinalysis, blood, urea, nitrogen, and blood sugar were normal. No X-ray change from previous report on orbits; chest films were negative. Excepting the eye findings, the neurologic examination was normal.

Course. A review of the pathologic slide suggested the possibility of a muscular dystrophy. On the basis of the inflammatory process previously reported, a course of streptomycin, aureomycin, and chloromycetin therapy was given. Following this, the chemosis decreased and the globe became more mobile, so the patient was discharged.

Fourth admission. On November 15, 1949, the patient was readmitted because the left eye was again chemotic and immobile (fig. 2). There was widening of the palpebral fissure, exophthalmos, chemosis of the lower bulbar conjunctiva, and ophthalmoplegia. The globe could not be pushed back into the orbit. There was some early staining of the

Fig. 3 (Bedrossian). Section showing numerous lymphocytes and some plasma cells collected about the blood vessels. There is also a marked degree of edema which has separated the bundles of muscle fibers. No degeneration of muscle fibers is seen.

cornea at the 6-o'clock position near the limbus. Vision was correctible to 6/9. Fields and fundus were normal. Exophthalmometer reading was 21 on 111 base line.

Laboratory. Blood count and urine normal. Blood sugar, 180 mg. percent; serum cholesterol, 260 mg. percent; creatine, 614 mg./935 cc. urine; creatinine, 1,131 mg./935 cc. urine. Basal metabolism rate, +13. Benz-Jones protein, negative.

Course. Left cerebral arteriography was performed and showed no tumor or aneurysm. Since a thyrotropic exophthalmos was now being considered, the slide was again reviewed and found to be quite consistent with the type of histopathology described in thyrotropic exophthalmos (fig. 3). Since the patient's one remaining eye was in grave danger, a left frontal craniotomy or Naffziger decompression of the orbit was

performed on November 22, 1949. The patient was also started on thyroid extract.

At the present time, the exophthalmos is diminished, but the edema has receded only slightly.

4501 State Road.

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HETEROTRANSPLANTATION OF TUMORS INTO VARIOUS REGIONS OF THE GUINEA-PIG EYE*

ALBERT C. SNELL, JR., M.D.
Rochester, New York

It is well established that some malignant tumors will survive and grow for a period of time when transplanted into the anterior chamber of the eyes of alien species. There have been numerous reports of successful ocular heterotransplantations of human and other mammalian tumors.[1-18] Frog carcinoma has been tranplanted into the anterior chambers of the eyes of alien species of cold-blooded animals by Lucké and Schlumberger.[19]

On the other hand, it is apparent that ocular heterotransplantations of malignant tumors fail more often than they succeed. This has been the experience of most of the authors reporting on this topic. Woglom[20] was unable to transplant mouse sarcoma to the eyes of rats. Morris, McDonald, and Mann[21] observed no unequivocal evidence that 40 human cancers grew when transplanted into the eyes of guinea pigs. Lushbaugh and Steiner[18] transplanted specimens of seven human malignant lymphomas, none of which grew.

In spite of many negative results, there is a considerable volume of evidence that the anterior chamber is a uniquely favorable site for the heterologous transplantation of cancer.

In searching for factors responsible for the superiority of the eye as a site for heterologous tumor transplantation, it is obviously useful to define the anatomic boundaries within which the superiority exists. Therefore, transplantations were made within various regions of the eye. The sites so tested were the anterior chamber, cornea, vitreous cavity, lens, and subconjunctival space.

Our criteria for growth in any of these areas require the fulfillment of two principal events: (1) The transplant must increase in size at least threefold; (2) the cells of the transplant must be identifiable as the same as those implanted.

A corollary of the first prerequisite is that all the observed instances of growth of a transplant in terms of size have been associated with vascularization in our experience. Sometimes a vascularized mass develops following an anterior-chamber transplant which is not made up of growing tumor, but of inflammatory tissue, so that increase in size and vascularization alone does not prove that a "take" has occured, and histologic preparations are necessary for identification.

This type of inflammatory reaction resembles only superficially an actual "take" in the living animal, and the distinction is usually obvious after a little experience.

A further possible source of error in interpretation is that some transplanted tumors exhibit no evidence of enlargement or vascularization or any activity which, on inspection of the living animal, might be interpreted as growth, and yet on histologic examination the specimen is morphologically intact and may exhibit mitotic figures.

Either gross or microscopic evidence alone may, therefore, be misleading. Both criteria must be fulfilled in order to establish proof that growth has occurred.

Assay of the growth-supporting capacities of the four intraocular transplantation sites was first carried out with a human breast carcinoma removed from a cerebral metastasis. The tumor was transferred to the guinea-pig anterior chamber, where it grew readily. This tumor and the technique used

* From the Divisions of Ophthalmology and Cancer Research, Department of Surgery, the University of Rochester School of Medicine and Dentistry. This work was supported by a grant from the United States Public Health Service.

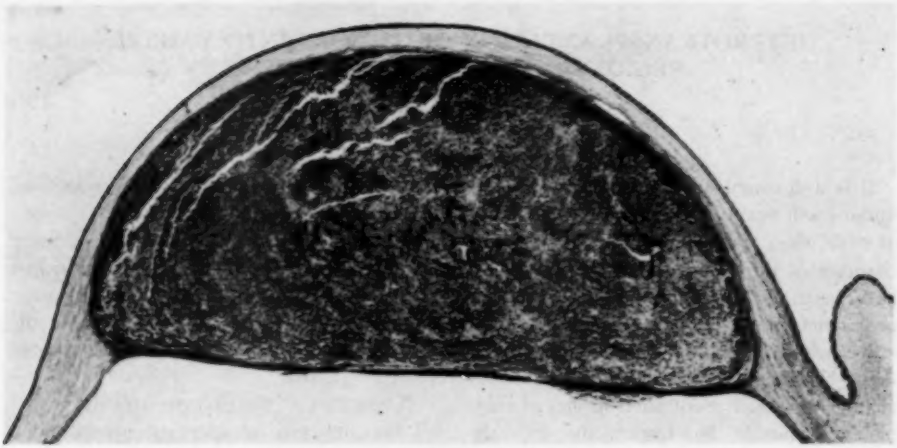

Fig. 1 (Snell). Growth of a transplant of human breast carcinoma at six weeks in the cornea of a guinea-pig eye.

in anterior-chamber transplantation have been described.[12]

When the anterior chamber was about half full of the tumor, the animal was killed, and bits of the intraocular tumor were passed to another guinea-pig. The tumor was kept alive in this way for a period of 22 months through 12 anterior-chamber passages, when it was finally lost. The tumor was transplanted into the anterior chambers of 194 guinea-pig eyes, and it grew in 115 (59 percent) of these.

In addition to the anterior-chamber transplantations, intracorneal inoculations of the same tumor were made into 41 guinea-pig eyes. For this procedure the material was prepared in the usual way, and the fragments of tumor were placed in the same blunt trocar used for the anterior-chamber transfers.

Fig. 2 (Snell). Growth of a transplant of human breast carcinoma at 14 days in the anterior chamber of a guinea-pig eye.

The recipient cornea was nicked but not penetrated with a keratome. A narrow semi-blunt spatula was introduced into the nick and could readily be made to pass tangentially between the layers of the cornea, creating a plane of cleavage. The spatula was then swept back and forth laterally, pivoting about its point of insertion, so that a pocket was formed between the layers of the cornea. The mouth of the trocar was introduced into this pocket, and the fragment of tumor discharged by the action of the trocar's plunger. The tumor could be tucked deeper into the corneal pocket by stroking the surface of the cornea. This procedure was carried out in 41 eyes.

Growth occurred in six of these (15 percent). When growth occurred, blood vessels from the limbus penetrated the cornea and supplied the transplant, which then developed a pink color and began to enlarge (fig. 1). Growth commenced two to six weeks after transplantation. The histologic characteristics were similar to those of the anterior-

chamber transplants (fig. 2).

The viability of the healthy-looking corneal growth was indicated by the fact that a representative specimen which had been growing for seven weeks in the cornea was transferred back again to the anterior chamber where it grew progressively in the usual manner.

None of the corneal growths attained the size of some of the anterior-chamber transplants, and all those which were not terminated underwent regression exactly as did the anterior-chamber transplants. It is apparent that the behavior and characteristics of the corneal transplants closely parallel those of the anterior-chamber transplants, with the difference that the incidence of "takes" is much reduced.

This difference may be due to extrusion of the transplants in some instances, or to the increased difficulty for the tumor to vascularize, since blood vessels are not at first in apposition to the tumor, as is the case when it lies against the iris, but must traverse part of the cornea in order to reach it.

Transplants were made into the vitreous cavity in 28 eyes. Vitreous transplants were introduced through a small scleral incision behind the ciliary body, using a trocar and plunger as before. The plants were readily observable through the pupil at the time of introduction, and could be examined subsequently in the same way.

None of the intravitreous transplants showed any evidence of growth similar to the successful anterior-chamber or corneal transplants. Enlargement or vascularization did not occur.

The period of observation was usually prolonged until the implant had disappeared and was not identifiable at autopsy or in histologic preparations. One preparation made six weeks after implantation, however, showed a recognizable bit of the tumor, the cells of which appeared to be degenerating (fig. 3).

In six cases transplants of the same tumor were introduced within the substance of the lens. To introduce transplants in this area

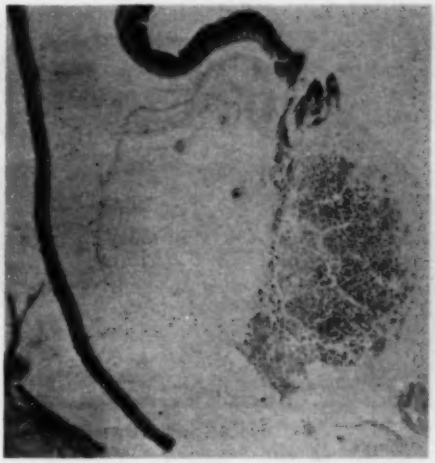

Fig. 3 (Snell). A degenerating transplant of human breast carcinoma at six weeks in the vitreous of a guinea-pig eye.

the tip of the keratome used in incising the cornea was made to penetrate the lens capsule. The trocar was then readily passed into the substance of the lens and the transplant deposited there. This resulted in the extrusion of the contents of the lens capsule and was associated with more than the usual amount of inflammatory reaction. No growth occurred.

Observations made on the ocular transplantations of the human breast carcinoma are summarized in Table 1.

The same intraocular transplantation sites were investigated with a second tumor, the readily transplantable mouse carcinoma MT8.[21] In the case of this tumor a con-

TABLE 1

RESULTS OF TRANSPLANTATIONS OF HUMAN BREAST CARCINOMA INTO VARIOUS REGIONS OF GUINEA-PIG EYES

Transplantation Site	Number of Recipient Eyes	Number of Transplants Showing Growth	Percentage of Transplants Showing Growth
Anterior Chamber	194	115	59.3
Cornea	41	6	14.6
Lens	6	0	0
Vitreous	28	0	0

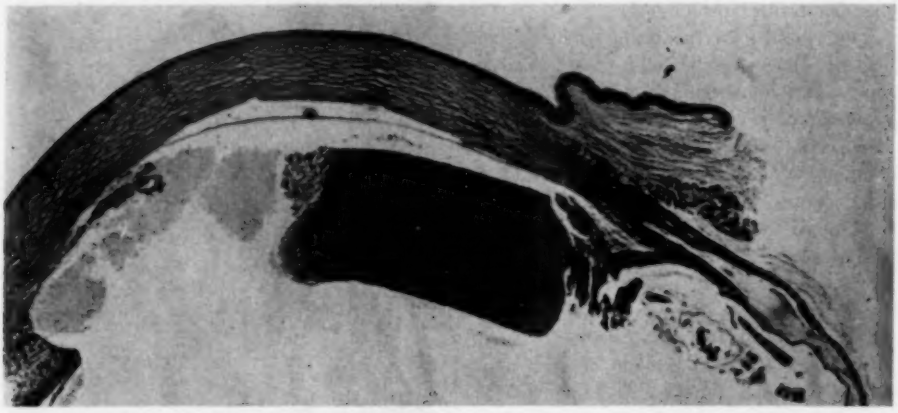

Fig. 4 (Snell). Growth of a transplant of MT8 at seven days in the anterior chamber of a guinea-pig eye.

tinuous supply was always available from the primary C3H mouse host in which the tumor was carried by serial subcutaneous transplantation. Our earlier experience with this tumor indicated an incidence of "takes" of 50 percent in a series of 40 eyes.

In the present series, first generation transplants to the anterior chamber of the guinea-pig eye grew in 17 of 38 eyes. Second or third anterior-chamber generation transplants grew in 32 of 65 eyes. In all, 103 eyes received MT8 transplants in the anterior chamber (fig. 4), and growth was observed in 49, or 47.6 percent.

Transplantations of MT8 tumor from the mouse to the guinea-pig cornea (fig. 5) grew in 14 of 22 eyes. Eleven corneas received transplants of MT8 which had been growing in the guinea-pig anterior chamber, and growth occurred in nine of these eyes. The

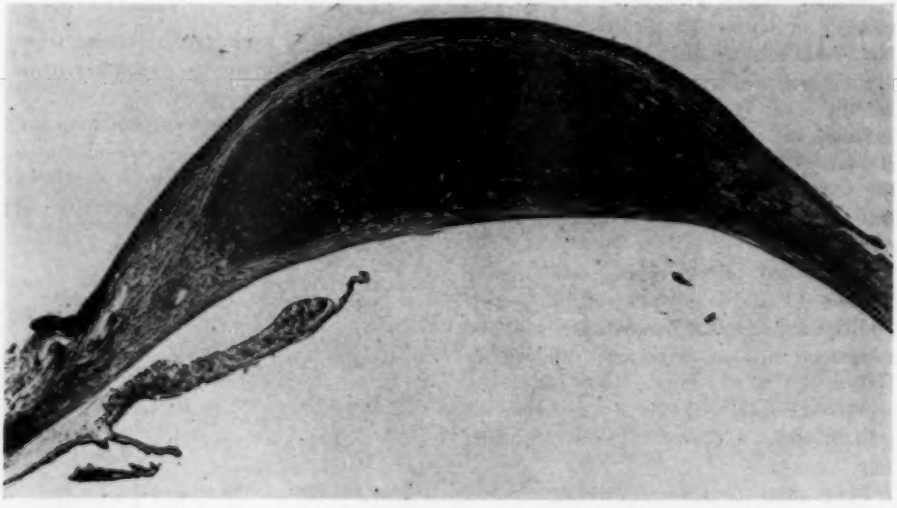

Fig. 5 (Snell). Growth of a transplant of MT8 at seven days in the cornea of a guinea-pig eye.

total number of corneas receiving MT8 transplants was 33; growth occurred in 23 of these, an incidence of 69 percent. The average maximum volume of the growing intracorneal transplants was less than that of the anterior-chamber transplants.

Transplantations of pieces of MT8 were made into the vitreous cavity of the guinea-pig eye directly from the mouse in six instances: No growth occurred. In an effort to improve the results, MT8 tumor which presumably had become adapted to the guinea-pig eye by one or more passages in the anterior chamber was used for the vitreous transplants in 18 additional instances. Again, no growth occurred.

Subconjunctival transplants of MT8 were made in 18 eyes. In placing these transplants the trocar was introduced through a small incision in the conjunctiva and passed a little distance from the incision, where the fragment of tumor was discharged.

The interpretation of the behavior of the subconjunctival transplants was complicated by the fact that they were partly obscured by the overlying conjunctiva, which lost most of its normal transparency due to the ensuing inflammatory reaction. This reaction reached its height in six or seven days, at which time the transplant was still identifiable and sometimes moderately enlarged. After this, the transplant shrank, the inflammatory reaction subsided, and in about five more days the conjunctiva was relatively uninflamed and the transplant had disappeared.

In comparison, anterior-chamber transplants of MT8 produced moderately severe corneal and conjunctival reactions, subsiding after three to five days without much change in the implant. Between the sixth and 14th day, and sometimes later, the implant vascularized and then enlarged and grew. Two of the 18 subconjunctival transplants of MT8 enlarged at least threefold and, as well as could be determined, appeared to be vascularized.

Since these animals were not autopsied at that time, proof is lacking that these two instances represented an actual growth of the tumor, although such is probably the case. The relationship between the subconjunctival and the intraocular sites requires further clarification.

Transplants of MT8 were made into the lens in 15 guinea-pig eyes. Unusually severe ocular reactions resulted and several of the eyes became completely disorganized. In others an occluded pupil or a total cataract prevented visualization of the transplant. However, in several instances, it has been possible to follow the course of the intralenticular transplant with the slitlamp and corneal microscope.

TABLE 2

RESULTS OF TRANSPLANTATIONS OF MOUSE CARCINOMA MT8 INTO VARIOUS REGIONS OF GUINEA-PIG EYES

Transplantation Site	Number of Recipient Eyes	Number of Transplants Showing Growth	Percentage of Transplants Showing Growth
Anterior Chamber	103	49	47.6
Cornea	33	23	69.7
Lens	15	0	0
Vitreous	24	0	0
Subconjunctival space	18	2 (?)	11.1 (?)

These implants have remained clinically inert without evidence of enlargement or vascularization and are being kept under observation. Survival in the anterior chamber of a transplant which is not growing is unusual for this tumor, and it appears that the position of the transplant under the lens capsule affords it some protection from the absorptive mechanism.*

This was the experience of Morris, McDonald, and Mann,[21] who observed survival of intralenticular tumor transplants for 13 to 64 days. Vascularization did not occur

* After this report was submitted for publication, tumor growth occurred into the anterior chambers of three eyes which had received intralenticular transplants of MT8.

and the transplants enlarged little or none.

Observations made on the ocular transplantation of MT8 are summarized in Table 2.

Summary and Conclusions

Heterologous ocular transplantations of a human breast carcinoma and of the mouse carcinoma MT8 were made into the anterior chamber, cornea, lens, and vitreous of guinea-pig eyes. Both of these tumors grew well in the anterior chamber, somewhat less well in the cornea, and not at all in the lens or in the vitreous. The mouse tumor failed to grow when transplanted under the conjunctiva except in two doubtful instances.

The capacity of the guinea-pig eye to support the growth of these cancers is shared by the anterior chamber and cornea, and not by the vitreous. Transplants made into the lens may survive for an undetermined period of time without growth or vascularization.

260 Crittenden Boulevard (20).

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RETINAL DETACHMENT

With special reference to preoperative subretinal drainage

John M. Wilson, M.D., Thomas P. McKee, M.D.,
and E. Malcolm Campbell, M.D.
Johnson City, Tennessee

Subretinal drainage is sometimes used as a diagnostic aid in the preoperative search for a retinal tear. We have found it to be of therapeutic value when used preoperatively to flatten a highly raised retina.

It is advantageous to find a retinal hole preoperatively, but in a bullous detachment that hole still has to be projected onto the sclera. This may be done theoretically by a complex set of charts and figures as devised by Cowan and McAndrews[1] or by the technique of Stine.[2] A retinal tear lying on or near the sclera can be more accurately projected onto the sclera.

A flat retina gives a much better surgical prognosis than a highly elevated one, not only because of the more accurate localization of retinal tears, as has been mentioned, but also because much less diathermy treatment is necessary to produce the desired adhesions between the retina and choroid.

For this reason, strict bedrest with both eyes bandaged or the use of pinhole goggles is practiced by most surgeons preoperatively in order that some absorption of the subretinal fluid may take place. This prolongs the patient's preoperative hospitalization.

After the diagnosis is made and the area of elevation and localization of the tear or tears are noted on the chart, our routine consists of admission of the patient to the hospital where he is placed on strict bedrest with both eyes bandaged.

The head is placed so that the elevated retina will be dependent. After 24 hours an ophthalmoscopic examination is done to note the effect of this eye immobility on the retina.

If there is still definite retinal elevation, we institute subretinal drainage. The sclera is bared over the highest point of elevation. A three-mm. incision is made through the sclera, care being taken not to injure the underlying choroid. A 6-0 silk suture is placed through each lip of the wound and the lips are sutured back on themselves to insure continued drainage. A punctum dilator heated to red heat is then plunged through the choroid and the subretinal fluid is drained.

The patient is put back to bed with a binocular bandage and with the detachment in the dependent position. After 48 hours the eye is again examined and the position of the tear noted, or if not previously found, another search is made.

A retinal reattachment operation is then performed. The sutures are removed from the scleral wound and the incision is temporarily sutured closed. We use the Weve surface diathermy over the area of detachment with particular care being made to seal the retinal tears. The first application is made at the estimated place of the tear and this is checked by an ophthalmoscopic examination. At the end of the operation, the scleral sutures are removed to allow continued drainage.

If, on the first examination after admission to the hospital, the retina is flattening out and is fairly flat after three days, the preliminary sclerotomy is not done, but is performed at the end of the operation.

Postoperatively the patient is kept in bed until the 14th day and discharged on or about the 18th day. He wears binocular dressings until he leaves the hospital and pinhole glasses for six weeks to two months.

We feel that this routine has several advantages: (1) Aids in the localization of

retinal tears preoperatively; (2) requires less diathermy therapy to produce the desired adhesions; (3) lessens the patient's stay in the hospital; (4) gives the patient the fortitude to go through with the operation.

We feel that this last point is very important. Two of our patients refused surgery when they were told that they would be in the hospital for a minimum of two weeks and incapacitated for approximately two months and with only a 50-percent prognosis of a good result. These patients consented to surgery when it was explained that a preliminary procedure would be done and, if it did not appear to help, they could leave the hospital.

After the retina is in place following the subretinal drainage, the patient is encouraged when he can see that the rough form field taken in bed has markedly improved and, in many cases, that large letters can be read with an eye that previously had no central vision.

Nine cases in which this regime was followed were treated at the McKee-Wilson Eye Hospital during the past year. This is a very small series from which to draw any definite conclusion; however, we feel encouraged since our results have been much better than previously. Eight of these cases were successful with the retina in place and a full field of vision.

Case reports

Case 1

P. R. C., aged 58 years, was admitted to the hospital on October 11, 1948, with a history of blurred vision in the left eye for the past two weeks. He had received a heavy blow on the forehead by a piece of lumber three weeks previously.

Examination revealed vision to be reduced to hand movements in the temporal field of vision. There was a marked bullous retinal detachment extending from the 12- to the 7-o'clock positions. No tear was found. He was put on complete bedrest.

The following day an incision was made through the sclera at the 5-o'clock position, 10 mm. from the limbus. The choroid was perforated and the subretinal fluid was drained. On examination two days later the retina was flat and the rough form field taken in bed was normal. He was able to read large print.

The following day a retinal reattachment operation was performed. His postoperative course was uneventful. When last seen on December 29, 1948, three months after surgery, the retina was in place, the field of vision was full, and the central vision was 20/70.

Case 2

M. C., aged 41 years, was first examined on October 22, 1948. He complained of poor vision in the right eye that had been discovered accidentally one week previously. He gave no history of trauma.

Examination revealed that vision was reduced to 20/80 in the right eye. There was a detachment of the retina with multiple small holes near the periphery. He refused surgery, but reconsidered two weeks later and consented to the preliminary operation.

He was admitted to the hospital on November 9, 1948, and the following day a scleral incision was made at the 6:30-o'clock position, 11 mm. from the limbus. The subretinal fluid was drained and the scleral lips were sutured back on themselves to assure drainage. Three days later the retina was in place and the rough field of vision had improved.

A retinal reattachment operation was performed. His postoperative course was uneventful. He was last examined on June 10, 1949, seven months after operation. The retina was in place, the field of vision was normal except for a cut in the superior field to 35 degrees, and the central vision was 20/80.

Case 3

L. A., aged 20 years, was first examined on December 28, 1948, while on Christmas vacation from college. She had discovered that the vision in the left eye was poor when she had a routine school physical examination in October.

On examination, vision in the left eye was reduced to 20/400. There was a detachment of the retina from the 3- to 7-o'clock positions. The detachment passed through the macula. There was a large disinsertion from the 5:30- to 6:30-o'clock positions. Immediate operation was advised, but she delayed it until she returned to school for her examinations.

On January 15, 1949, a sclerotomy opening was made at the 5-o'clock position, 13 mm. from the limbus, and the subretinal fluid was drained.

On January 18, 1949, a retinal reattachment operation was performed. Her postoperative course was uneventful. She was last examined on January 3, 1950, one year after operation. The retina was in place, the field of vision was full, and her central vision was 20/200.

Case 4

Mrs. J. H., aged 52 years, had on February 3, 1949, an intumescent cataract removed from the right eye intracapsularly through a round pupil. An erisophake was used and a small amount of vitreous was lost as the lens was being delivered.

On her 10th postoperative day she slipped on the floor and struck her head on the radiator.

On examination there was no evident damage to the eye. On March 3, 1949, two weeks following the accident, she noticed a cloud before the right eye.

Examination revealed a large bullous detachment of the retina from the 10- to 2-o'clock positions, with a horseshoe-shaped tear at the 10:30-o'clock position. She was readmitted to the hospital and put on complete bedrest.

Two days later, on March 5, 1949, the retina was flat, therefore, preoperative subretinal drainage was not performed. At the end of operation an incision was made through the sclera and the subretinal fluid was drained. Her postoperative course was uneventful.

When last examined on January 3, 1950, 10 months after surgery, the retina was in place, the field of vision was normal, and the corrected vision was 20/25.

CASE 5

B. A. B., aged 55 years, was referred to us by a colleague. He had been treated for glaucoma for several years previously. An iridencleisis had been performed on the right eye with a good result. The left eye had been previously controlled by pilocarpine and furmethide.

When these drugs failed to maintain normal tension, his physicians decided to try DFP. One drop of the 0.1-percent solution was instilled on May 10, 1949. The action of this drug presumably caused such intense ciliary spasm as to cause a disinsertion of the retina. He was first seen by us the following day.

Examination. Vision in the right eye was 20/60. Vision in the left eye was hand movements, superiorly and temporally. There was a large bullous detachment from the 12- to 3-o'clock positions. No tear was found. He was put to bed on his left side for three days. On May 14, 1949, the retina was flat; preoperative subretinal drainage was not therefore, performed. We were still not able to see the disinsertion at the ora serrata, but we were confident this was present because of the history following the use of DFP.

A retinal reattachment operation was performed and a scleral incision made for the drainage of subretinal fluid. His postoperative course was uneventful. He has been followed carefully for the past 10 months and at no time has his tension risen above 18 mm. Hg (Schiøtz). He has had no medical treatment for glaucoma. The retina is in place, he has a full field of vision, and his central vision is 20/30.

CASE 6

C. C., aged 50 years, had, on January 31, 1949, an intracapsular cataract extraction on the right eye through a round pupil. There was no vitreous loss. His postoperative course was uneventful and his vision was corrected to 20/15.

On June 9, 1949, he reentered the hospital complaining of a cloud over his right eye. He had jumped from a cherry tree the previous day.

Examination. There was a large bullous detachment of the retina from the 9- to 12-o'clock positions. No tear was found. He was put to bed on his right side. Two days later the retina was flat so preoperative subretinal drainage was not instituted. We were still unable to find a tear.

The usual retinal reattachment operation was performed, followed by a sclerotomy. He was last seen on September 30, 1949, three months following surgery. The retina was in place, he had a full field of vision, and his vision was corrected to 20/20.

CASE 7

Mrs. J. H. B., aged 75 years, was first seen on August 30, 1949. She complained of poor vision in the left eye for the past month. There was no history of trauma.

Examination revealed a large bullous detachment of the retina from the 12- to 4-o'clock positions. She was put to bed on her left side. On September 2, 1949, the retina was still markedly elevated; therefore, the subretinal fluid was drained. Two days later the retina was in place and the usual retinal reattachment operation was performed.

The postoperative course was uneventful. She was last examined on December 1, 1949, three months following surgery. The retina was in place and the field of vision was full. The central vision was less than 20/400 due to marked macular degeneration.

CASE 8

M. D., aged 72 years, this patient was first examined on September 20, 1949. She had a bullous retinal detachment from the 8- to 1-o'clock positions. There was a round tear at the 10-o'clock position. She was put on strict bedrest. The following day a sclerotomy was performed at the 11-o'clock position and the subretinal fluid was drained.

On September 25, 1949, the usual retinal reattachment operation was performed. On October 22, 1949, the retina was in place at the area of detachment and the hole was sealed. However, there was a detachment of the entire lower half of the retina. No new tear was found. Her central vision was 20/100.

This patient should have had a second operation, but due to her advanced age we did not encourage further surgery.

CASE 9

J. L., aged 54 years, had an intracapsular cataract extraction through a round pupil on his left eye on March 24, 1949. His postoperative course was uneventful. His vision was corrected to 20/20.

Eight months later, on November 23, 1949, he suddenly noticed a reduction of vision in his left eye. He had noticed flashes of light before this eye one week previously.

Examination revealed a bullous detachment of the retina from 11:30- to 3:30-o'clock positions. No tear was found. He was put to bed on his left side.

When examined the next day, the retina was flattening. Two days later the retina was flat, therefore, the subretinal fluid was not drained preoperatively. We were still unable to find the tear.

A retinal reattachment operation was performed. A sclerotomy opening was made at the 2-o'clock position for subretinal drainage. When examined three days later, it was found that he had suffered a gross vitreous hemorrhage. The vitreous gradually cleared.

He was last examined on March 10, 1950, three and one-half months postoperatively. The vitreous was clear except for many vitreous opacities. The retina was in place, the field of vision was full and the central vision was corrected to 20/50.

Comments

Of the nine patients, preoperative subretinal drainage was carried out in five. In the other four the retina flattened out rapidly and did not require preliminary treatment.

Retinal tears were found in only five cases.

The age of these patients varied from 20 to 75 years with an average age of 53 years.

This series includes three aphakic eyes occurring in 174 cataract extractions or 1.7 percent. This is a slightly high percentage, but in 438 cataract extractions performed by us in the past four years we have had a total of four detachments or 0.91 percent. This is in keeping with Duehr's[3] percentage of 0.8 percent. He reported 16 detachments in 1,750 cataracts performed at the University of Wisconsin. Two of our cases had definitely associated trauma and one had vitreous loss at the time of the operation. One case occurred eight months after surgery, one six months, and one after one month.

The case caused by DFP was very interesting. This man had a definite uncontrolled glaucoma before his detachment, but since that time his tension has been normal. The diathermy was applied only eight mm. from the limbus because it was assumed that this was a case of disinsertion at the ora serrata. We believe that this procedure had the affect of a cyclodiathermy operation.

Summary

1. Nine cases of retinal detachment are reported.

2. The importance of converting a highly elevated retina into a flat one preoperatively is stressed. If bedrest does not accomplish this, it is suggested that the retina be flattened by subretinal drainage preoperatively.

3. We feel that surface diathermy with a flat electrode gives the best surgical results.

4. One case of retinal detachment caused by DFP is reported.

207 East Watauga Avenue.

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ACHROMATOPSIA*

Report of two cases

Robert L. Alexander, M.D.
Cleveland, Ohio

Total color blindness—by some called monochromatopsia, and by others, achromatopsia—is a rare anomaly. There are apparently two individual anomalies described as total color blindness, each having some different sign and symptom but having one common factor—a loss of the ability to distinguish different colors of the same intensity.

The larger number of cases fall into Group 1. These patients have visual acuities of 6/60 or less; a dazzling of vision or photophobia on exposure to light of higher intensities; a nystagmus which is searching in quality and decreases in subdued illumination; a spectrum shortened at both ends; a maximum intensity deviated from yellow toward green, and an increase subjective perception in twilightlike illumination.

The remaining, and smaller number, constitute Group 2. They have visual acuity of 6/60 or better and few or no symptoms of nystagmus, no dazzling or photophobia on exposure to light of higher intensities, and little or no change of visual acuity in different intensities of light. These persons, however, experience total color blindness with a shortening of the spectrum and a deviation of maximum intensity from yellow to green.

In 1926, Julia Bell[1] in her exhaustive work reported 119 cases recorded up to that time on the continent, in England, and in North America. She approached the subject from a genetic standpoint. Since then many other cases have been added to the literature; this has resulted in isolated reports of patients with absence of color vision without grouping or accounting of the patients observed.

Some of the cases reported have been tested by most delicate means using highly technical equipment that was especially designed for testing color vision and photopic vision; for, in this time, there has developed a concurrent interest in scotopic, photopic, and chromatic vision as related to the total color blind.

Cases in the literature

A survey of the literature from 1926 to 1946 gives 38 cases in which visual acuity was 6/60 or less and in which photophobia, nystagmus, twilight vision, and total color blindness were present. In addition, many of these cases showed a movement of the luminosity from yellow to green and a shortened spectrum (Beach,[2] three cases; Holm and Lodberg,[2a] 23 cases; Lewis and Mandelbaum,[3] three cases; Sloan and Newhall,[4] one case; Waardenburg,[5] three cases; Wagner,[6] three cases; Wolfflin,[7] one case; Walsh,[8] one case). My two cases, herein reported, bring the total to 40 cases.

There is a second group of 17 cases in which there is total color blindness but in which one or more of the following factors is lacking: a visual acuity of 6/60 or less, nystagmus, photophobia, and twilight vision (Best,[9] one case; Fry,[10] one case; Geldard,[11] one case; Heinsius,[12] one case; Macgillivray,[13] one case; Sloan and Newhall,[4] two cases; Sloan,[14] one case; Waardenburg,[5] five cases; Walsh,[8] four cases).

There was also a group of four cases, reported in the literature as totally color blind, which did not present sufficient data to permit their classification either as typical or atypical cases of total color blindness (Baetjer,[15] one case; Bennett,[16] one case; Bonnet and Rollet,[17] one case; Wright,[18] one case).

* From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

Case reports

My two cases of achromatopsia may be classified as totally color blind. Both patients displayed: (1) A complete inability to perceive chromatic light; (2) visual acuity of less than 6/60; (3) shortening of the spectrum; (4) severe photophobia in high illumination; (5) nystagmus; and (6) an apparent decrease in the central vision.

The first patient was a well-developed, well-nourished white woman, aged 32 years, whose physical examination, X-ray studies, and blood studies showed no congenital anomalies. No pathologic condition was found.

The second patient was a well-developed, well-nourished white woman, aged 34 years, whose physical examination, X-ray studies, and blood studies showed neither congenital anomalies nor pathologic condition.

TABLE 1

Responses in perimetric tests

Object at Center	Object at 10°	Response to Object at 10°
25 mm.	35 mm.	Looked brighter
35 mm.	25 mm.	Looked brighter
25 mm.	45 mm.	Looked brighter
35 mm.	45 mm.	Looked brighter
45 mm.	35 mm.	Looked brighter
45 mm.	25 mm.	Looked brighter

The patients, introduced to me from the practice of Dr. Lorand V. Johnson, were sisters. The findings were identical in all examinations except that of the lens. Patient 2, had a posterior polar and posterior capsular opacity of the left lens.

Physical findings of the eyes of both patients were:

Visual acuity of each eye was ability to count fingers against a black background at 100 cm. and against a white background at 30 cm. Photophobia was present in all luminosities except that of a twilight quality. A coarse, horizontal, pendular nystagmus was present.

The corneas and conjunctivas were clear to gross and slitlamp examinations. The iris stroma was normal to slitlamp examination. The pupils were symmetric and reacted to light and accommodation. The lenses by slitlamp examination were normal except for Patient 2. The media were clear.

Ophthalmoscopic examination revealed normal discs and blood vessels. The retinas were without hemorrhage or exudate. The macular regions appeared normal but, because of the nystagmus and photophobia, they could not be minutely studied. The refractive error found after a cycloplegic refraction did not improve the visual acuity of either patient.

Both patients noted that blinking afforded better vision just after opening the eyes.

Attempts were made to test the perimetric and tangent-screen responses under standard conditions, but at no illumination could consistent findings be elicited. Because of this no central scotomas could be found by these means. Using white standard test objects of diameters of 25 mm., 35 mm., and 45 mm. against a black tangent screen with a light intensity of five foot-candles on the screen the patients had the responses, using either eye (the other eye being covered), shown in Table 1. These findings would seem to indicate a diminution of central vision.

In another test, Dr. C. W. Williams' lantern for testing color vision was used. The test was done at three meters in a room with light of less than one foot-candle. With the room lighter and the lantern at a greater distance the patients could not see the test lights. They could not name a single color, describing what they saw only as bright, warm, or cold colors.

When green, white, and blue were exposed at the same time with equal background light, the patients saw them as the same color but of different degrees of brightness. When red, green, and red were exposed at the same time with equal background light, the patients stated that they were the same color, but the middle color, green, was the brightest. Testing was also attempted with the Ishihara color plates, but the pa-

tients' visual acuity was too low to observe them.

For the final test, an arc-light spectrum was projected on a solid white background and superimposed known pure color lights were projected on this spectrum. In this way a method of calculating the patients' response was obtained.

Each patient described the spectrum as a rectangle of bright light which was brighter in the middle (5,461 Angström units) and stopped abruptly at both ends (about 4,960 and 5,770 Angström units). This indicated that their bright line was in the green range, and that there was no red spectrum stimulation and little blue spectrum stimulation.

These tests demonstrated that both patients had poor visual acuity, nystagmus, photophobia, hemeralopia, a shortening of the spectrum with a shift from yellow to green, and a decreased central vision.

A third sister and the mother had visual acuity of 6/6, and a perfect score with the Ishihara color plates and the Williams' lantern. Both have refused further examination. Two brothers and the father of these patients are dead. The family insists that the brothers' and sisters' eyes have been good. The mother denied any consanguinity.

A total of 61 authenticated cases (including the two in this paper) of total color blindness have been reported in the literature since 1926. Of these cases, 40 show typical total color blindness; 17 atypical; and four cases remain unclassified. They are reported in sufficient detail to suggest the possibility that there is more than one type of color blindness. Some of the patients had a visual acuity of 6/60 or better and were totally color blind; some had a visual acuity of 6/60 or less and were totally color blind. The reasons why such variations in visual acuity should occur in color blindness are not known. There are theories, however, that seem to suggest an answer.

Discussion

The early theories of color vision recognized the fact that there is some relationship between subjective perception of color and certain energy wave stimulations. The early theories, therefore, pointed to a light-sensitive organ which was responsive to a definite wave stimulation. This led to the later idea of a specific end-organ sensitive to a specific stimulation.

The fundamental facts of the physiology of color vision, such as the law of color existence, did not allow one element to mediate all colors. Hence a hypothesis of three primary colors was developed with each primary color having a single element sensitive to itself.

This instigated the ideas of Thomas Young,[19] who postulated that each primary color had a kind of nerve fiber which translated that color and that combinations of these sensations produced the other colors. Sensations of all colors combined produced white light. The primary color sensations he chose were red, green, and blue.

Helmholtz[20] elaborated Young's theory and it became known as the Young-Helmholtz theory of color vision. This theory postulated three different light receptors, each having a specific photochemical response for some one portion of the spectrum, with a limited response to the entire spectrum. In this way, red, green, or blue produced a primary sensation, and an equal stimulation by certain combinations of these colors produced the remaining visible colors. The color white was produced by equal stimulation of every color, and black was the result of no stimulation.

During this time, the theory of duplicity or duplexity developed, based on the observations of Purkinje.[21] Purkinje reported in 1825 that colors matched for brightness in high luminosities were not valid in low luminosities. He noted that a shade of yellow-green was the brightest color in bright light, but in twilight, green or blue-green was the brightest color.

Schultze,[22] studying the Purkinje phenomena, suggested that it was due to two

different receptor cells in the retina acting under different conditions. He introduced the duplicity theory. By histologic investigation Schultze demonstrated that the anatomy of the retina was divided into rods and cones.

Von Kries[23] studied the Purkinje phenomena and suggested the rule of rods and cones in vision. He theorized that the rods had a maximum of sensitivity in the green wave lengths and subdued light, and that the cones were sensitive to brighter light intensities.

The Young-Helmholtz theory failed to explain certain anomalies in color vision such as the sensation derived from a mixture of certain colors, relative color blindness at the periphery of the retina, and the ability of the periphery of the retina to perceive different intensities of gray, yet have a good perception of white.[24]

Hering[25] introduced a psychologic theory to explain the fundamental sensations that brought about color vision. This theory proposed three pairs of mutually antagonistic sensations; red vs. green; white vs. black; and yellow vs. blue. These sensations were produced by katabolism and anabolism. Destruction or katabolism produced by light of certain wave lengths caused the sensations of green, black, and blue. When this light stimulation was removed, the sensation was built up (anabolism) and produced the complementary colors of red, white, and yellow. A balance of katabolism and anabolism produced a sensation of gray.

Katabolism in one type of cell resulted in a photochemical reaction of red, and anabolism in the same type of cell produced the sensation of green. If the colors of red and green were exposed with equal intensity, they balanced each other, inasmuch as they are antagonists.

These, the Young-Helmholtz theory and the Herring hypothesis, have comprised the most commonly quoted explanations of color vision and have best withstood adverse criticism. They have in common the supposed existence of substances or sensory receptors in the retina that respond to stimulations in light of different wave lengths. The theories have been supported by more recent observations on the responses of the eye to light under different conditions such as light response under scotopic and photopic states. An expansion of the theory of duplicity has thus followed more complete and careful examination of the rods and cones.

The cones have been analyzed as the receptors of light wave stimulations under conditions of light adaptation. The rods have been analyzed as the receptors of light-wave stimulations under conditions of dark adaptation. Selig Hecht[26] extensively reviewed and documented this subject in 1937. The physiologic evidence of the retinas, demonstrated by many clinical experiments, showed that in the rod-free area of the fovea there is the absence of a colorless interval and of Purkinje's phenomena. The rod areas of the retina showed a visibility curve of scotopic vision. The absorption and bleaching of visual purple found in the rods corresponded to this curve.

The use of dark adaptation to study cone and rod vision has attained importance since Sloan,[4] Hecht,[26] and others have shown that, in a normal eye after six minutes, the cone curve reaches it low, and after a lag of about thre minutes, the dark-adaptation curve again plunges downward. This first is attributed to the dark adaptation of cones, and the second to that of rods.

Wald[27] has further contributed the fact that hydroxy-carotenoid, or xanthophyll, which can be extracted from the fovea of a human eye, responds to light absorption in a manner similar to that of cones. He again confirmed the fact that rhodopsin, which comes from the rods, reacts as the rods do to light absorption. The close relationship of rods and cones is important, in his opinion, to normal dark-adaptation curves.

Repeated experiments[13, 14, 22, 28] have shown that the fovea has no Purkinje phenomena and that, in eyes well adapted to the

dark, the rods are 100 to 1,000 times more sensitive to the light of standard low intensities than the cones.

This establishes that the retina has both rods and cones, but does not explain the cone's selective sensitivity to colors. Though color sensations are attributed to cones, there have been no more complete explanations than those of Young-Helmholtz and Herring. These are based upon end-organs that sometimes mediate at least three primary sensations.

Adler[24] quoted authors who have shown that, on putting red light in one eye and green light in the other, the resulting sensation is yellow. He says, "This indicates that colors actually have their origin in the brain and arise from the stimulation of receptors in the retina."

This thought is also presented by Adams,[29] a psychologist, who believes that color visualization is a perception of anabolic and katabolic activity on receptor cells integrated by a synapse after the primary cone and rod stimulation, and which is carried to higher centers for interpretation. Such a theory may be more fully substantiated by histologic evidence as presented by Polyak.

Polyak,[28] in his extensive observations, found that in the pathway of the rods and cones there exists one important difference. The rods lack "midget bipolar" cells, intermediary neurons which the cones contain. This may mean that the response to the short-wave portion of the spectrum and the achromatic rod vision is caused by a lack of reaction to higher wave lengths due to deficiency of the Polyak cells.

These concepts have been strengthened by observing certain patients who are totally color blind. Those who have been examined for dark adaptation have shown two types of curves. A small group has a high visual acuity with a curve almost the same as that of a normal eye. Patients with a low visual acuity show curves similar to the dark adaptation of normal rod vision.

Patients whose dark-adaptation curve followed that of a normal rod dark-adaptation curve also have the visual pattern found in the normal dark-adapted eye. This group has little central vision, a shift of the bright line of the spectrum toward the short-wave end, the inability to perceive chromatic color, and photophobia. Such patients are said to be without color vision or achromatic. They are the ones with cases of typical total color blindness.

Achromatic vision may be attributed to Polyak's findings of lack of "midget" cells, Adams' similar suggestion of a synapse response only to rod stimulation, or Adler's implication that color actually arises in the brain and that rods do not stimulate the color-receptive centers of the brain.

The explanation of atypical complete color blindness then assumes a different aspect. Those patients in this group have good central vision. They also have a dark-adaptation curve that is not completely that of rod response. They recognize only changes in the intensities of light, not hues. The patients actually see one type of light and are monochromatic in color vision. Crisp[30] doubted that these cases should be classed with the typical group.

The explanation for the condition in this latter group has been attributed to a conduction-pathway, or higher center, defect. This could be true of the patient—a laboratory worker—described by Larsen,[31] who evidently must have had a visual acuity of better than 6/60 to be employed. Larsen, in his famous paper, reported her to have a normal distribution of rods and cones, but there were atypical cones in the fovea.

Furthermore, in the normal eye there is no evidence of the different types of cones described by the Young-Helmholtz theory or Herring theory. This suggests that the defects could easily be in the conduction pathway or higher perception centers.[32] Those in this atypical group might see the different intensities of color but be subjectively unable to appreciate them as hues. These patients have been shown to match the differ-

ences of color intensities not by hue but by matching two different colors of the same intensity.

Sloan and Newhall[4] and Lewis and Mandelbaum[3] agreed that the classical form of total color blindness, achromatopsia, is a lack of retinal function in which the cones, if present, do not function but that the light perception found is rod function. However, they do not agree on the cause of atypical color blindness or monochromatopsia.

Lewis and Mandelbaum[3] believe that monochromatopsia is based on the triceptor theory of color vision in which three colors function, and which is given the common name of trichromatic vision.

Three different types of cone cells are required, each containing a pigment which is photosensitive to a selective set of energy waves. Stimulation of all the cones would produce trichromatism and stimulation of only two types of cones would produce dichromatism; stimulation of only one type of cone would produce monochromatism.

In the latter case, in which only one type of cone functions, there would be only one response to the stimulation of the color spectrum and no comparison of the stimuli. This would result in a monotone of color with its greatest mental reception dependent on that type of cone stimulated.

This, they believe, would show the patients were not color blind, but only sensitive to one color and thus have cone visual acuity, a cone visibility curve, and a maximum spectral brightness of cones. The patient would have monochromatic color vision and be atypically totally color blind.

Sloan and Newhall,[4] on the other hand, believe atypical color blindness or monochromatopsia is a defect in the higher centers or in the conduction pathways rather than in the retina itself. By "retina itself," they appear to refer to the receptor cells of the retina. They agree in part with Polyak that the defect might be in the type of bipolar cell of the retina. This theory also accords with the theory of Adams, previously cited, that the defect may be attributed to a synapse of the bipolar cells in the inner retinal cells.

Thus the atypical cases of total color blindness coincide with the histologic evidence presented by Polyak or Larsen. Polyak demonstrated that in the normal eye the rods lack the *h*-bipolar cell, and Larsen has shown that cones are present in the totally color blind. This suggests that cones may lack the cell in atypical retinas and act as rod receptors of light stimulation.

All theories recognize the fact that the defect is one in cone function, but the cause of the anomaly has not been established. If the cause could be proved to be in the end cells of the cones, in the pathway of the cones, or in the higher integrating centers of the cones, perhaps all abnormal color responses could be explained easily.

The variant facts suggested during recent years indicate that new evidence must be found and new hypotheses introduced to explain congenital total color blindness. The clinician must differentiate between two types of total color blindness in order that more may be understood about case histories and their accompanying discussions.

Summary

Thirty-eight authenticated cases of typical total color blindness, achromatopsia, have been reported in the literature between 1926 and 1946. The two cases reported for the first time in this paper bring the total to 40 cases. Seventeen authenticated cases of atypical color blindness, monochromatopsia, have been reported in the literature in the same 20-year period. Four cases have been reported in the literature that could not be classified because of lack of data. Additional cases are mentioned in the literature, but these cannot be authenticated at this time.

Conclusion

A division of total color blindness into two major groups, achromatopsia and mono-

chromatopsia, is suggested on the basis of clinical signs and symptoms.

Two hypotheses are advocated: (1) The cause of typical achromatopsia lies in the cones pathways; (2) the cones act as rod receptors.

Euclid Avenue and East 93rd Street (6).

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NOTES, CASES, INSTRUMENTS

AN ELECTRIC COAGULATOR*

H. Rommel Hildreth, M. D.
Saint Louis, Missouri

The eye surgeon is seldom troubled by bleeding. Oozing is bothersome at times, and once in a while it becomes necessary to stop frank bleeding. The surgeon calls for the alcohol lamp and uses the "hot hook," a rather medieval procedure. The "hook" is either too hot or too cold and, of course, the lamp cannot be used in the presence of the more frequently used general anesthetics.

In order to control the bleeding from the small vessels of the sclera, it is necessary only to coagulate, not to cauterize, the tissues. The "hot hook" too often will actually cauterize the parts and leave an eschar to be absorbed, delaying healing. This is especially undesirable when dealing with the wound itself.

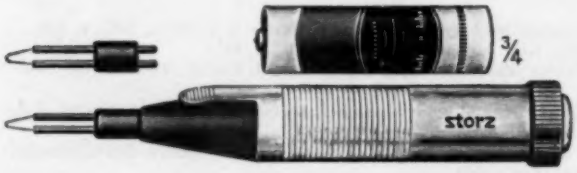

Fig. 1 (Hildreth). Electric coagulator. The tip fits in place just beyond the switch.

The electric coagulator is presented as an instrument for controlling hemorrhage. It is designed primarily to stop the bleeding from scleral vessels.

The handle contains one small dry-cell (pen-cell) for power. When the switch is pressed, the tip becomes hot almost instantly. The heat is adequate to coagulate, but no cauterization takes place.

Sterilization of the instrument is done simply by putting it in Post's solution along with the other instruments. The battery is inserted first and the end screwed tight, and it may be changed during an operation, if necessary, without contaminating the outside handle.

There is no danger of explosion in the presence of a general anesthetic. Sparking does not take place, and the tip will not ignite the anesthesia vapor.

As stated above, the tip heats up almost instantly. The switch therefore should be released as soon as possible, for the power drops rather soon if the current is left on. For the few moments at a time that the heat is required the battery will hold up well if fairly new. Its power recovers overnight or simply with rest periods between operations, but it is well to use a fresh battery fairly often if ample heat does not develop at once.

When coagulating a single bleeder, the tip is placed on the point immediately after sponging. If one wishes to control a line of oozing points, as at the limbus, after freeing a conjunctival flap, the tip should be slowly "brushed" across the region. To stop oozing from a scratch incision or deeper wound, the side of the tip may be placed directly in the cut with the current on for a few moments.

It is necessary to have the field dry. A pool of blood will dissipate the heat so rapidly that coagulation of the cut vessels will not take place. For this reason the instrument does not work very well in muscle and lid surgery. A fresh battery and adequate sponging will help. It is useless, though, to plunge the tip into a bloody field.

There are definite limitations to the use of

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* From the Department of Ophthalmology, Washington University School of Medicine. Presented as a new instrument at the 55th annual session of the American Academy of Ophthalmology and Otolaryngology, October 1950, Chicago.

This instrument is manufactured by Storz Instrument Company, 4570 Audubon Avenue, Saint Louis 10, Missouri.

this instrument. The coagulator was developed primarily to fulfill one need—namely, to coagulate the bleeding vessels of the eyeball proper without cauterizing the tissues. If a cautery instrument is desired, there are many on the market already.

The coagulator went through a number of stages before this final form. At first a transformer was used instead of the battery in order to give a more constant source of power. The nuisance of the wires and their sterilization was so great as to make the instrument impractical and really not worth the bother. Larger batteries and more than one cell were tried along with a variety of tips, but in the operating room the small single-cell type that can be sterilized so easily seemed best.

3720 Washington Boulevard (8).

A PERIMETER FOR RETINAL LOCALIZATION*

ARYEH FEIGENBAUM, M.D.
Jerusalem, Israel

No method, however ingenious, of retinal localization can claim to be perfect. Errors come in when, by the necessary assumption of schematic eyes, the different sizes of an eyeball and the different shapes of a detached retina occurring in praxi, are not taken into account. Nevertheless, a preliminary perimetric localization with indirect ophthalmoscopy is of primary importance, even if it has to be confirmed or slightly modified during operation by yet another means of determination.

Two primary conditions are required when attempting retinal localization at the perimeter: (1) Good fixation of the patient's head in a comfortable sitting position, as only in this way can be measured the exact amount of rotation of the eyeball without an additional rotation of the head; (2) as little interference as possible by the parts of the perimeter with (the indirect) ophthalmoscopy.

A perimeter which I have used for this purpose with very satisfactory results for the past 14 years is herein described (figs. 1 and 2). The dimensions are approximately those of a light hand perimeter. As usual, a fixed quarter-arc carries at one end the axis of the perimeter and the perimetric arc; at the other end is the chinrest. Instead of a handle (placed as a spare part below the table, Figure 1) there is an iron rod (about 30 cm. long), placed within the metal tube fixed to the table.

The arc of the perimeter, as well as the fixed quarter-arc are as narrow as possible, one cm. or even less (as much as is compatible with the stability of the arc); both arcs have a graduation on their convexity. The center, opposite the patient's eye, carries a small mirror, and at the outside a nonrotating circle (also made as narrow as possible) is fixed with a pointer, to indicate the meridian.

The chinrest is as in a regular perimeter. The headrest can be lowered or raised and its plane can be given the inclination necessary to suit the patient's forehead.

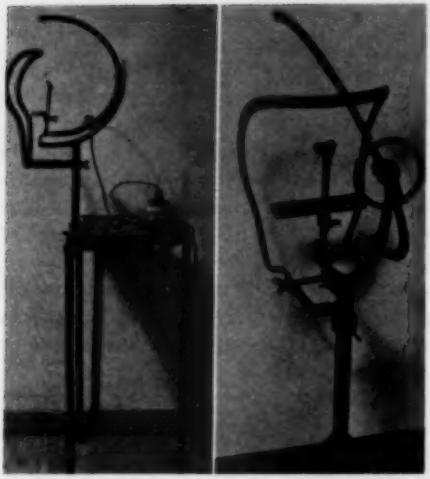
The table, on three legs, to which the perimeter is attached is a half-circle and as narrow as possible. One precaution must be taken in order to counterbalance the weight and pressure of the patient's head: the hind leg of the table has to be heavily weighted. After everything is well adjusted, the patient is seated as comfortably as possible.

In conformity with the calculations of Colenbrander (1931) and Stine (1934), the simplified tables (Tables 1, 2, and 3) can be used for determination of the limbus distance on the retinal arc. In Tables 1 and 2 the simplification up to 50 degrees is Colenbrander's.

PROCEDURE

While the other eye is covered, the patient is advised to look with the eye being examined at a white mark (piece of leukoplast)

* From the Ophthalmologic Department, Hadassah University Hospital.



Figs. 1 and 2 (Feigenbaum). A perimeter for retinal localization.

put on the concave side of the perimetric arc at a convenient distance from the center in order that the observer need not be compelled to throw his (reflected) light from extreme positions. If the patient's vision is too low, a small electric bulb may be used as a mark (fig. 1) or, in extreme cases, the patient's finger tip may be placed at the chosen spot (while his arm is well supported).

If, for example, the tear is in the upper and outer periphery, the patient is advised to look upward and temporally at the white mark (electric lamp or the finger tip) which is affixed on the perimetric arc, say at 40 degrees; the latter is rotated into the corresponding meridian (let us say 45 degrees). When the observer's light falls exactly on the localized spot upward and temporally and can, at the same time, be projected on the graduated arc at 15 degrees below the center, this makes an angle of 55 degrees, which (according to Table 1) is equal to a limbus distance of 15 or 14 mm. respectively (in the 45 degree meridian).

The calculation can also be made without the use of the tables if one remembers that, in normal eyes, a limbus distance of seven or eight mm. has to be considered; in aphakic eyes, five mm.; in high-degree myopia, nine mm. (when the spot to be localized in the latter instance is situated anteriorly to the equator).

Taking the example already quoted, we would have to subtract 55 degrees from 90

TABLE 1

NORMAL EYES

Angle of incidence (observed angle)		90°	80°	70°	60°	50°	40°	30°	20°	10°	0°
Limbus distance (in mm.)	Nasal	8	10	12	14	16	17.5	19	21	22	23
	Temporal	7	9	11	13	15	17.5	19	21	22	23

TABLE 2

APHAKIC EYES

Angle of incidence	90°	80°	70°	60°	50°	40°	30°	20°	10°	0°
Limbus distance (in mm.)	5	7.5	10	12.5	15	17	19	21	22	23

TABLE 3

HIGH DEGREE MYOPIA

Angle of incidence	90°	80°	70°	60°	50°
Limbus distance (in mm.)	9	9.5	12	13	15

degrees which gives 35 degrees. Reckoning a one-mm. limbus distance for each five degrees thus found, this would make seven mm. to which we would have to add eight or seven mm., respectively, for the limbus distance in eyes with medium refraction, with the final result of: 15 or 14 mm. projected limbus distance, or five mm. (result: 13 or 12 mm.) in an aphakic eye; and nine mm. (17 or 16 mm.) in a high-degree myopic eye.

15 Abyssinian Street.

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TRANSFORMER, RHEOSTAT, AND SWITCH INSTALLED IN AO GIANTSCOPE CASE*

CLEMENS KIRCHGEORG, M.D.
Neenah, Wisconsin

The installation of a transformer, rheostat, and switch in the case for the AO giantscope facilitates the use of the instrument. Compactness, weight, and ease of handling were governing factors in the design.

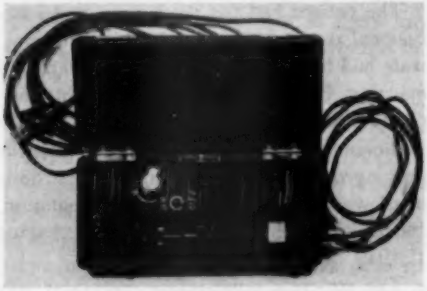

Fig. 1 (Kirchgeorg). The complete installation.

As shown in Figure 1, the case has been rearranged. The transformer, rheostat, and switch are enclosed in an aluminum and wood compartment which is screwed to the case—the switch panel is of pressed wood. The switch is on the 110V circuit so that, when shut off, no current is in the transformer.

The transformer is rated at 6.3 volts, so that at its peak use there is caused an overload on the ophthalmoscope light. This overload of light is an asset in examining dense or hazy media, as well as when using filters. Short use when overloaded does not appreciably lessen the life of the bulb.

The 110V wire is about 15 feet in length and is wrapped around the case, a very quick and easy method of putting it away.

104 North Commercial Street.

* From the Wills Eye Hospital, Philadelphia, Pennsylvania.

MERCURIAL DISCOLORATION OF THE EYELIDS*

JOHN C. LONG, M.D., AND RALPH W. DANIELSON, M.D.
Denver, Colorado

Pigmentation of the skin from the repeated local application of various metallic compounds has been occasionally described. Apparently the first report of pigmentation from mercury was that of Goeckermann.[1] He described a series of cases of discoloration of the skin of the face resulting from the prolonged use of face creams containing mercurous chloride.

Later, Goeckermann,[2] in a supplementary report, described the findings of a skin biopsy in such a case. Small pigment granules were found in all layers of the skin and in

* From the Department of Ophthalmology, University of Colorado School of Medicine.

the subcutis. The granules were entirely removed from sections of skin by a solution of iodine, suggesting that they were compounds of mercury.

Hollander and Baer[3] described a woman whose face and neck were a dirty grayish black. She had been using a cream containing mercury for 15 years. A biopsy of the skin of the neck showed no evidence of globules of metallic mercury or of any other foreign particulate matter at the magnifications available. Mercury could be recovered from a particle of skin by a delicate electrochemical technique.

The patient was treated by the application of tincture of iodine followed by alcohol. This resulted in a decrease in pigmentation but the patient did not complete the treatment.

Recently, several observers have reported staining of the skin of the eyelids from the therapeutic application of mercurials. Abramowicz[4] described a bluish-gray discoloration of the skin of the eyelids resembling "exaggerated make-up" in a woman who had applied white precipitate ointment of 6.6 percent nearly nightly for 41 years.

In addition there were dark pigment granules in the bulbar conjunctiva, especially near the cornea, with a preferential distribution around the perivascular lymph vessels. The peripheral cornea in the region of Descemet's membrane showed a discoloration varying from a greenish-gray to a bluish-gray. There was a yellowish-brown lusterless opacity in the pupillary area of the lens.

Wheeler[5] presented five cases of pigmentation of the skin of the eyelids following the prolonged and daily use of ointments containing either mercuric oxide or ammoniated mercury. Four years was the shortest period of application. Wheeler stated that there appeared to be a direct etiologic relationship between the mercury and the pigmentation, and that the color faded slowly after discontinuing the ointment.

M. H. Post, Jr.,[6] in the discussion of Dr. Wheeler's paper, reported the case of a woman who had been applying yellow mercuric oxide, 1.0 percent, to her lids for 25 years. She presented a sharply demarcated dark band on the upper and lower lids. One year after stopping the application the pigment was much less extensive and only about one half as dark as formerly.

Report of case

The patient, a white woman, aged 74 years, was observed on August 1, 1949. The skin of the lids of both eyes showed a striking slate-gray discoloration extending from the rima in all directions for somewhat over one centimeter. The pigmentation was perhaps more intense in the folds near the outer canthi.

Slitlamp examination with the high power suggested the presence of almost subvisible black particles in the folds of transilluminated skin. Her friends had several times suggested that the appearance was produced by the application of cosmetics.

The patient had for years been under occasional treatment for blepharitis. Silver nitrate had been infrequently applied to the lid margins. For 15 years, she had nightly applied a one-percent yellow mercuric oxide ointment to the lids. It was thought that the prolonged use of the mercuric oxide ointment was responsible for the pigmentation. Its use was therefore terminated on August 1, 1949.

The patient's outstanding complaint was the inability to keep the eyes open without special effort. It was felt that this complaint might arise, at least in part, from a redundance of skin of the upper lids. It was thought that the excision of some of the skin from the upper lids might make the patient more comfortable and, at the same time, provide material for microscopic and chemical studies.

Excision of skin from the right upper eyelid was carried out under procaine anesthesia on December 19, 1949. A strip of skin approximately 4.5 mm. wide was excised along the entire length of the upper eyelid.

At the time of the excision the patient had used no mercury for 4.5 months and it was our impression that the pigmentation had faded somewhat. The excised skin was divided into several portions for study.

Histologic examination

The outstanding feature is the presence of very numerous fine brownish-black pigment granules. The pigment is found distributed in the superficial part of the corium, often immediately beneath the epidermis. Some of the granules are arranged in a linear pattern, following the course of the collagen fibers. Pigment is found in the cytoplasm of the fibrocytes.

The densest accumulations of granules are found phagocytized in mononuclear cells which defy positive identification because of the amount of pigment in the cells. The pigment granules are best seen with the high-power or oil-immersion lenses. They measure from less than one micron to over two microns in diameter. The epidermis is almost entirely free of pigment, nor is there any special concentration of pigment around the glands.

Microchemical examinations

Paraffin sections of tissues fixed in picric acid saturated with hydrogen sulfide (method of Almkvist-Christeller[7]) showed the characteristic granules, perhaps blacker than in the formalin-fixed specimens. This test was intended to demonstrate mercury as a black precipitate of the sulfide. Since the untreated granules were brownish-black, the difference in color after sulfide treatment was not striking.

The same lack of conclusive identification was found with the method of Lonbardo-Debendetti,[7] in which an acidified solution of stannous chloride is used to reduce mercuric compounds to metallic mercury. The minute size and the opaque nature of the particles made the distinction difficult. Unsuccessful, also, and probably for the same reason, was the method of Brandino[8] in which a violet precipitate is formed with diphenylcarbazide.

Fig. 1 (Long and Danielson). Mercury pigmentation of skin of eyelids.

Treatment of sections with a compound solution of iodine results in the complete removal of the pigment granules from the tissues.[2, 9]

Chemical determination

A small piece of skin was submitted to Mr. Evan Campbell, Division of Industrial Medicine of the University of Colorado, for chemical study. A very sensitive variation of the dithizone quantitative method of Kozelka[10] for the microdetermination of mer-

Fig. 2 (Long and Danielson). Multiple pigment granules in skin of upper eyelid. (×650.)

cury was employed. A strip of undried skin approximately 2.0 cm. long and 1.5 mm. wide, with a weight of 0.0428 gm., yielded 0.004 mg. of mercury.

Conclusion

The frequent and prolonged application of mercurial ointments to the lids may result in a slate-gray pigmentation of the skin. In the case reported minute granules, giving a presumptive test for mercury, were found in the cutis in large numbers. Mercury could be detected in the skin by a quantitative analytical method. The pigmentation appears to be quite harmless and slowly fades after application of the ointment is stopped.

227 16th Street (2).

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A LINEAR LIGHT TARGET FOR DIPLOPIA FIELD TESTS*

David Kadesky, M.D.
San Francisco, California

A linear light target for use in testing diplopia fields is presented. This instrument has distinct advantages over a point source of light:

1. A small amount of diplopia which might be interpreted as a blur with a point source of light will be demonstrated as true diplopia with a linear light test object.

2. By changing the axis of a linear light source, discrimination of vertical and horizontal deviations is facilitated.

3. The presence of torsion of a linear image will immediately be apparent when the linear test object is used.

The linear light source or target designed for the testing of diplopia fields and cyclophoria is shown in Figure 1. It consists of a pocket flashlight equipped with a No. 222 Mazda condensing globe and a lucite rod, six inches long and one-fourth inch in diameter, encased in a metal tube which exposes one face of the rod. This provides a sharply defined linear light 5.75 inches in length. The encased rod is detachable so that the flashlight may be used for general purposes or

Fig. 1 (Kadesky). Photograph of linear light test object.

* This instrument is made by the Parsons Optical Laboratories, Inc., San Francisco.

may be provided with additional fittings such as plastic transilluminating cones or a cobalt filter for fluorescein patterns.

The linear light source may be used with the red-glass test for plotting routine diplopia fields. As a further refinement, when torsional defects are suspected, it may be used with the Maddox double prism with a red glass over either eye.

Greens' Eye Hospital (9).

ACRYLIC CORNEAL IMPLANT IN KERATOPLASTY*

ISTVÁN GYÖRFFY, M.D.
Budapest, Hungary

Acrylic implants are more and more widely used in all branches of plastic and reconstructive surgery. They are so well tolerated and so excellent from a technical point of view that they are supplanting every other material.

These qualities and the good results obtained in surgery gave us the idea of using them instead of corneal grafts in keratoplasty. Our method is not intended to be used in every single case. By substituting plastic for human cornea we hoped for a good result only in cases in which the transplantation had to be made in dense, cicatricial corneal tissue, where there was little hope of a human graft remaining alive and clear. It was also to be expected that, because of the reduced vitality of a mass of scars, the cicatricial cornea would better bear the mechanical pressure due to the fixation of the plastic graft.

Professor Imre performed this operation in 1942. For this experiment we chose a patient, a man aged 36 years, who had suffered severe burns from lime on both eyes years before. Both eyes showed a thick, cicatricial leukoma. Vision in the right eye, which was to be operated on, amounted merely to good perception of light; in the left eye it was 1/10 through an optic coloboma. The tension of both eyes was normal.

The structure of the corneal implant and

Fig. 1 (Györffy). Cross-section of the corneal implant.

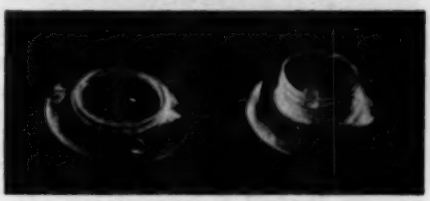

Fig. 2 (Györffy). Full view of the implant.

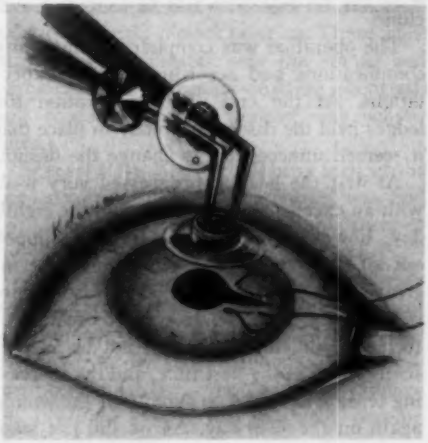

Fig. 3 (Györffy). Introduction of the implant.

the operative technique of its placing is clearly shown by the illustrations. The implant itself differs from the normal corneal graft 3.5 mm. in diameter, in that it has a fixation ledge above and below which presses it into the cornea. The lower ledge and the implant are in one piece; the upper one is

* From the II. University Eye Clinic.

Fig. 4 (Györffy). Fixation of superior disc by rotation.

screwed on. The outward and inward surface of the implant is optically ground to such a dioptry as to correct the calculated refraction to emmetropia. It was made and ground in the contact lens laboratory of the clinic.

The operation was completed without any complications and according to our expectations. At the end of the operation the ledges held the disc so perfectly in place that it seemed unnecessary to change the design.

At first the healing progressed very well, with an excellent visual result. On the eighth day, however, half of the implant slipped out of the wound, the tension having increased in the meantime. Professor Imre replaced the implant. However, because of technical difficulties it could not be as perfectly fixed as the first time, and the increasing tension caused it to slip out of the wound again on the 13th day. As we did not want to carry on further experiments with the patient, we covered the opening with a conjunctival flap, whereupon the cornea again healed by cicatrization.

Since the implant did not remain in its place (probably on account of increased tension), our experiment ended unsuccessfully. It is a question, however, whether it was not the eye which was unsuitable, as it had a tendency to hypertension from the beginning. Further it may be that, if the increased tension had proved to be transitory only and the fixation had been more perfect, the disc would not have slipped out but would have healed into the wound.

To all these questions our case brought no answer and, since we could not make any further experiments due to the war and postwar difficulties, we could not find out the cause of the displacement.

From a theoretical point of view the perfect optical effect of the plastic corneal implant is a great advantage; nor will it lose its transparency. There is also less danger of formation of a retrocorneal membrane, such as often forms behind a human graft.

Although our case was not successful we believe that soon a method will be found which will provide a definite solution to this problem.

VIII. Bródy Sándor u. 10.

SPONTANEOUS IDIOPATHIC HOLES IN THE SCLERA

CHARLES A. TURTZ, M.D.
New York

Holes may appear in any part of the sclera. These develop slowly and may be single or multiple. Large deficiencies may be formed by the coalescence of smaller ones. Occasionally a yellow excrescence may be found and, if punctured, yields a granular detritus. These holes may be covered by conjunctiva or, in some instances, the area can be seen laid bare without any herniation.

If the holes are formed over the anterior chamber, a cystic formation may be evident and a direct fistulous channel could be formed. If a fistula is formed, a conjunctival flap operation is indicated. Oast, in 1937, found beneficial results from ultraviolet rays.

The case I am reporting is unique in that a hole appeared in the sclera, directly at the limbus at the 12-o'clock position. The area was exposed without any conjunctival cover-

ing. This condition became chronic and was accompanied by pain and marked ciliary injection. It resisted treatment for many weeks and finally cleared up completely.

A similar hole appeared in the opposite eye at the corneoscleral junction at the 12-o'clock position. This also cleared up after many weeks of treatment.

Case report

Mrs. E. W., aged 38 years, a healthy woman without any previous history of any eye diseases, consulted me on April 30, 1946, and gave a history of pain and redness of the left eyeball of three weeks' duration. No treatment of any kind was given during that time. Her past history was entirely irrelevant.

Her visual acuity was 20/20 in the right eye, and 20/30 in the left eye. The appearance of the right eye, including a funduscopic examination, was entirely negative. An examination of the left eye revealed two pinpoint specks on the cornea, which stained with fluorescein. There was a moderate degree of ciliary injection. Fundus findings were entirely negative.

Atropine was instilled; penicillin ointment was applied; sodium salicylate was prescribed internally; and the eyeball was patched. She was also advised to apply heat at frequent intervals. For several days after the use of atropine, the pupil did not dilate fully; nor did it even after the use of adrenalin packs.

An examination with the slitlamp microscope revealed no posterior synechias. Blood chemistry, including a Wassermann test, was entirely negative. Chest X-ray films and Volmer tuberculin test also proved negative.

On May 23rd, a hole about two mm. in diameter, appeared at the corneoscleral junction, exactly at the 12-o'clock position. The uvea was clearly visible. This area became wider in a few days, despite local treatment of penicillin, atropine, applications of three-percent tincture of iodine, and injections of foreign protein.

The scleral hole resisted all forms of treatment and appeared to spread in diameter. On May 26th, a cherry red cautery was applied lightly at the margins of the hole and, several days later, the conjunctiva completely covered the hole; the ciliary injection gradually cleared and the eyeball became white. The patient was discharged on July 22nd.

She returned on October 19th, complaining of redness and irritability of the opposite eye (right). An examination revealed a moderately injected eyeball (ciliary). The cornea was clear; the fundus entirely negative. The same treatment—atropine, penicillin, and heat—was employed. The pupil did not dilate fully even with adrenalin packs. Proteolac injections were given without any appreciable difference in the appearance of the eyeball.

She was observed at frequent intervals and, on December 20th, a bulge of conjunctiva was seen at the corneoscleral junction, exactly at the 12-o'clock position. There were also corneal infiltrates near the limbus and temporally. An atropine reaction occurred, and scopolamine (0.5 percent was substituted).

Several days later, a hole was seen at the corneoscleral junction. The cornea was laid bare, and there was an exact duplication of the clinical picture of the opposite eye.

The same procedure was repeated—cherry red cautery lightly applied. Improvement was almost instantaneous. The hole was covered over by the conjunctiva. Improvement continued for several days; by January 24, 1947, the eyeball had gradually become completely white.

When I saw her on April 1, 1948, both eyes were white and she said that she had no irritability of either eyeball. At the sites of the former holes, a few bands of connective tissue, were barely visible.

Comment

In September, 1948, this patient developed paracentral scotomas and was admitted to

the Medical Center Neurological Institute under the care of Dr. Melvin D. Yahr. A complete neurologic study was negative. The scotomas cleared up several weeks later.

Scleromalacia perforans, described by van der Hoeve, is characterized by the appearance of holes in the sclera without dominant signs of any inflammation. It usually occurs in elderly people suffering from rheumatoid arthritis or gout. The pathologic findings are similar in every respect to those of the nodules found in the skin of patients suffering from rheumatoid arthritis.

In this case, the patient was a young healthy woman, who had no evidence of any rheumatoid arthritis or gout. The holes in her sclera were accompanied by pain, marked ciliary injection, and corneal infiltrates. In scleromalacia perforans, there are usually no accompanying inflammatory signs.

Summary

A case of idiopathic spontaneous holes in the sclera has been presented. The interesting features were the exact duplication in the opposite eye several months later, the poor dilatation of the pupils with atropine or adrenalin packs, and the marked ciliary injection. It was only after a hot cautery was lightly applied that a complete closure of the hole resulted.

65 Central Park West (23).

DISCIFORM KERATITIS TREATED WITH AUREOMYCIN

C. Keith Barnes, M.D.
Fort Worth, Texas

The clinical picture of disciform keratitis requires no detailed description. The condition has presented a therapeutic challenge in the past; many cases have progressed obstinately for months until a final vascularized scar has seriously damaged the vision.

Whether the etiology is truly viral has yet to be established; dendritic keratitis may be a herpetic variant. Superficial epithelial erosions and superficial punctate keratitis may be other variants.

The following three cases may provide a contribution to corneal therapeutics by reporting the use of aureomycin in corneal disease.

All three cases were first seen during a single month in a large industrial plant. No typical case of disciform keratitis had been diagnosed at this plant during the preceding year. Dendritic keratitis of greater or lesser degree was seen quite often, as were superficial epithelial erosions and superficial punctate keratitis. Because the dendritic keratitis responded excellently to the instillation of aureomycin, it was thought reasonable to try the drug in disciform keratitis. The total plant personnel averages around 16,000 men; the three patients were from widely separated areas in the plant.

Report of cases

Case 1

J. B. N., a white man aged 26 years, had a minute particle of aluminum alloy removed from the left cornea. The eye became increasingly painful and he was seen by referral on the fourth day.

The findings were typical for disciform keratitis. The lesion occupied a central area about one half of the corneal diameter, with marked lentiform thickening, wrinkles in Descemet's membrane, white clustered dots and water-cleft optical phenomena in the stroma, scattered large greasy keratic precipitates on the central endothelium, intense injection of the bulbar conjunctiva, and a trace of aqueous ray.

The lesion was as round as a coin. By retroillumination, it displayed a striking double-ring reflex like a bull's-eye target, the anterior ring appearing larger.

The patient was given one-percent atropine drops, three times daily, for cycloplegia and 0.5-percent aureomycin borate solution, to be instilled every hour while awake. The lesion began to resolve at once, and the patient resumed work seven days later with no visible evidence of the lesion except a few remaining keratic precipitates.

Case 2

C. W. S., a white man, aged 40 years, had a minute particle of fiberglass removed from the left cornea. The eye remained irritated and he, too, was seen by referral on the fourth day.

The findings were: a round central patch of irregular epithelium, central keratic precipitates, a trace of aqueous ray.

He was given a prescription for atropine but when he returned on the following day, the presence of disciform keratitis had become obvious. Aureomycin-borate (0.5 percent) solution was ordered every two hours topically, with hot compresses and atropine. The cycloplegia was very poor, and was occasionally encouraged with a neosynephrin drop.

Ten days later there was only moderate improvement. The poor dilatation made one suspect the potency of the atropine solution which had been obtained at a remote suburban pharmacy. A fresh solution of atropine dilated the pupil promptly, and the lesion resolved in another 12 days.

CASE 3

O. A. F., a white man, aged 62 years, had a moderately severe burn of the right eye from an analine-dye compound. The chemical burn had occurred before but, on this occasion when it failed to improve, he sought aid, also on the fourth day.

The conjunctiva was edematous and markedly reddened, the lids swollen, the pupil a trifle smaller than its fellow. There were a moderate number of central large, greasy, white keratic precipitates. Two scars from old healed ulcers were visible near the limbus (herpetic?). The intraocular pressure in both eyes was on the borderline of normal.

He was given a prescription for four-percent homatropine solution and, since he firmly insisted upon continuing work where no convenient refrigeration was available for aureomycin, he was given sulfathiazole ointment with instructions to return the next day.

He returned one week later, however, at which time the disciform keratitis was obvious. He was changed from homatropine to atropine, which he obtained from the same pharmacy as Case 2. Again he refused to stop work to use (refrigerated) aureomycin.

Two days later there was still no improvement, so he reluctantly accepted aureomycin to be taken to work in a thermos bottle. The cycloplegia was very poor and, at the end of his fourth week, there was no improvement. At this time the atropine used in Cases 2 and 3 became suspect, and both patients were given fresh supplies.

This patient stopped work, began instilling the aureomycin every two hours, and started hot compresses; 13 days later his corneal lesion was almost completely resolved.

CONCLUSIONS

Obviously few valid conclusions can be derived from three cases, but certain similarities deserve consideration:

1. All three cases came from the same industrial plant.
2. All three cases sought aid on the fourth day.
3. All three cases followed trauma.
4. Aureomycin borate solution (0.5 percent, topically) seeming to be effective in controlling the disciform keratitis in from seven to 13 days after the beginning of effective medication.
5. Effective atropinization with a fresh stock of the drug continues to be necessary.
6. No reactions to topical aureomycin were seen.

921 Neil P. Anderson Building (2).

OPHTHALMIC MINIATURE

In 1766 Lavoisier, in studying certain questions upon the lighting of Paris, which had been given for competition by the Academy of Sciences, found after several attempts that his sight wanted the necessary sensitiveness for observing the relative intensities of the different flames he wished to compare. He had a room hung with black, and shut himself up in it for six weeks in utter darkness. At the end of that time his sensitiveness of sight was such that he could distinguish the faintest differences.

Fernand Papillon, *Light and Life*, 1873.

SOCIETY PROCEEDINGS

Edited by Donald J. Lyle, M.D.

COLLEGE OF PHYSICIANS OF PHILADELPHIA

Section on Ophthalmology

March 16, 1950

Dr. Wilfred Fry, *chairman*

Orbital apex—Sphenoidal fissure syndrome

Dr. I. S. Tassman presented four cases of this syndrome. A pathologic process involving the bones at the apex of the orbit may produce pressure on the structures which pass through the sphenoidal fissure and the optic canal as they enter the orbit.

Syphilis and inflammation of the bones of the orbit arising in the nasal sinuses especially may produce ocular impairment, but perhaps a more important and not infrequent cause is a malignant process involving the sphenoid bones secondarily, by extension from a primary seat in the paranasal sinuses. Such a pathologic condition is of interest to the ophthalmologist, although the primary disease may be far advanced when it comes to his attention.

Ptosis and ophthalmoplegia are the most important and earliest manifestations of this syndrome and result from the pressure on the structures which enter the orbit through the sphenoidal fissure.

The sphenoidal fissure transmits principally the third, fourth, and sixth cranial nerves; the ophthalmic vein; the orbital branch of the middle meningeal (when it does not pass through the middle meningeal foramen) and the sympathetic fibers from the cavernous plexus; the sympathetic root of the ciliary ganglion, and sometimes the sensory root of the ciliary ganglion.

Various degrees of visual impairment result from pressure on the optic nerve as it enters the optic canal. The latter is closely related medially to the sphenoidal sinus and sometimes to a posterior ethmoidal air-cell. Often only a very thin plate of bone separates the optic canal from these. At times the canal makes a ridge inside the sinus. Not infrequently, the sinus or a posterior ethmoid air-cell may invade the small wing of the phenoid to a more or less degree, and they have been known to surround the canal completely.

The optic canal transmits the optic nerve, the ophthalmic artery, branches of the sympathetic carotid plexus, and the orbital prolongations of the meninges which form the sheath of the optic nerve. The complete sphenoid-optic canal syndrome, therefore, indicates involvement primarily of the second, third, fourth, and sixth cranial nerves, the ophthalmic division of the fifth nerve, sympathetic fibers, the ophthalmic vein, and the ophthalmic artery with corresponding clinical manifestations. When the syndrome is incomplete, the optic nerve or some of the other structures are spared.

This condition has been described at various times in the past as "the sphenoidal fissure syndrome," "syndrome of the posterior orbit," and "the orbital apex-sphenoidal fissure syndrome." In Dr. Tassman's opinion, the name "sphenoidal fissure-optic canal syndrome" would designate the site of the lesion and its symptom complex more accurately.

The four cases presented illustrated the occurrence of complete ophthalmoplegia with this syndrome. All had a fatal termination. In the first three, there was extension of a carcinomatous process from the nasal sinuses. In the fourth case, the primary site was in the naso-pharynx. This syndrome should be suspected, and the primary cause looked for, as early as possible. Careful X-ray examination of the nasal sinuses is important as an aid in the diagnosis.

In nearly all cases, the ocular involvement

occurs when the process is far advanced, and the middle fossa are already involved. The patients are usually about 60 years of age, and recurring nosebleed with nasal symptoms are complained of early. Pain and headache are common and early complaints.

The ocular manifestations are evidenced by impairment of vision, impairment of rotation, and ptosis, usually on one side which may later become bilateral. The third, fourth, and sixth nerve, with portions of the fifth, are involved as they enter the orbit through the sphenoidal fissure. The optic nerve is usually involved just as it enters the optic canal.

Discussion. Dr. Edmund B. Spaeth: I would very much like to discuss this paper for two reasons. First of all, because of the dismal prognosis as Dr. Tassman gave it, and, secondly, because of the differential diagnosis. If the prognosis is bad in most all cases, then it seems that the differential diagnosis is especially important.

One could spend 40 pages in differential diagnosis alone. Certainly that which is outstanding is to differentiate this orbital apex syndrome from sphenoidal ridge meningioma and from the cavernous sinus syndrome. Those two conditions have much in common with the orbital apex syndrome.

Dr. Tassman's presentations were all cases of malignancy. The diagnosis, I would say, would be rather difficult if it were not for the finding of a primary lesion and the X-ray manifestations of the orbital apex syndrome as an extension. Because of that, one might wonder whether, with an earlier diagnosis, the mortality could not be reduced if that orbit were to be cleaned out, and radiation therapy used.

One of his cases, I think it was the third one, might well have been a chiasmal syndrome of vascular pathology of the Circle of Willis. It seems that differential diagnosis in this situation is of outstanding importance. Any condition with as tragic a prognosis as this seems to have need for every effort possible for earlier diagnosis, and for some different form of therapy, surgical or radiologic.

Retrolental fibroplasia

Dr. Algernon B. Reese, New York, the guest speaker, presented this paper.

When the incidence of retrolental fibroplasia showed such a large increase around 1943, we were uncertain as to the correct definition of the disease. Gradually the disease is standing out as an entity separate and apart from other simulating conditions such as persistent hyperplastic primary vitreous and retinal dysplasia.

The indications are that some pathologic condition exists in the retina of affected infants even at birth and that this serves as a predisposing factor or matrix for the progressing lesion. At about the third to the fifth week, we note the tremendous dilatation and tortuosity of the retinal vessels, hemorrhages in the retina and vitreous, gradual detachment of the retina, and the development of fibrous tissue in the anterior vitreous. This active course is over at about the fourth to the fifth month, and then we deal with the residuum of the disease.

The indications are that vitamin E is not effective in preventing or arresting the disease. We are employing X ray at the early stages, but so far we have not had sufficient experience with it to warrant any conclusions. We are also using ACTH, as others are doing elsewhere, but it is also too early to give any assessment of this therapy. The attempt to excise surgically a sufficient amount of the pupillary tissue to permit some vision has not been encouraging. We believe that about 10 percent of the cases have been benefited some, but to so slight a degree that we are reluctant to do the operation.

Discussion. Dr. John S. McGavic: I have nothing really to add to Dr. Reese's splendid discussion of that group of conditions which make up the most pressing and exciting diseases in ophthalmology of today.

This is one subject which most of those present have seen develop in importance since they took up ophthalmology. Reading the articles of 1942 and 1946 is like trying to get around postwar Germany with a prewar Baedeker; the landmarks are almost completely changed.

The other evening I read in chronological order all of the articles I could find, ending with Dr. Reese's article in the AMERICAN JOURNAL OF OPHTHALMOLOGY for January, 1950, on "Retinal dysplasia." I have already asked the graduate students to read this and heartily recommend it to all as the most lucid brief review of the subject to date.

I cannot stress too much the value of reviewing this literature. This is one great opportunity to witness in a short space of time the way in which various syndromes and diseases have been elucidated in the past. The modern technique of attacking such problems would amaze our forebears in medicine. Tracing the emergence of a new entity should be an inspiration to all of us. Terry, Owens, Krause, and others have done a tremendous amount of work, and more is now being done throughout the country.

It is my impression, from all the descriptions which I have read and from the sections which I have seen, that we must be dealing with an inflammatory process. By this, I have in mind—inflammation in its broadest sense; that is, it may be an inflammation, based on bacterial or viral disease; or inflammation secondary to a lack of some fundamental nutritional element. Perhaps prematures are more susceptible to minor traumas of life.

In any event, the development of the fundus picture and the reaction of the vitreous described by Owens and Owens, and by others, certainly indicate some inflammatory reaction. The role of hemangiomas in the development of these various types of retrolental tissue remains to be determined. In any event it is a very interesting idea.

I am sure you are aware of two things after hearing Dr. Reese's address:

1. That histopathologic studies are necessary to assure a common denominator in our discussions. This has been lacking in the presentations of some authors so that we cannot be sure that we were talking about the same thing.

2. That Dr. Reese has done a great deal clinically, and has made the most valuable contribution of anyone in classifying the various types of retrolental tissue aberrations on a firm basis, proven by combined clinical and histopathologic studies.

Dr. William O. LaMotte, Jr.: I shall not prolong an already long but very interesting and instructive evening except to add my expression of appreciation to Dr. Reese for coming down here, and helping to clarify this very complicated subject for us. It did occur to me that he warned us how didactic he might be about this. He may well have been at times, but certainly tonight he gave us a very humble and detailed history of his interesting work on this subject, and I think we shall look to this kind of work in the future for the answer to this problem.

Dr. Harold G. Scheie: I had had no intention of mentioning ACTH in the therapy of retrolental fibroplasia until Dr. Reese referred to our work. Dr. Tyner and Dr. LaMotte have been routinely following the cases in our nursery; I have seen them in a more or less advisory capacity.

We recently had one such patient who developed retrolental fibroplasia while taking vitamin E. In desperation we considered giving the child X-ray therapy, but Dr. Pendergrass, professor of roentgenology at the University of Pennsylvania, opposed the idea. He did so because of the vital area of the child's brain which would very likely be affected by scattered irradiation, as would some of the paranasal sinuses. He was particularly apprehensive because of the sensitivity of the tissues of a premature infant.

While discussing possible therapy with the pediatric service, Dr. Joseph Stokes suggested that the child be treated with ACTH. This was started very shortly, and it was our

impression that the condition became arrested.

Before treatment, the child presented the typical picture of early retrolental fibroplasia consisting of markedly engorged retinal veins with peripheral retinal detachment. ACTH therapy was continued for about two weeks during which time the process seemed to become stabilized. Treatment was then stopped, and no further change occurred for at least another four weeks. At that time the child developed a severe dermatitis which prevented examination for a period of several weeks.

When the eyegrounds could again be seen, the retinal detachment had not progressed, but the central vessels had become displaced, emerging from the temporal aspect of the disc, suggesting an incipient retinal fold. A short time after this, the child died from pneumonitis. Evaluation of the effect of ACTH is not only impossible with a single patient, but it must be remembered also that progress of the condition can stop spontaneously.

Although this child's course suggested arrest of the retrolental fibroplasia as a result of ACTH therapy, we do not feel prepared to state so with any degree of finality.

Dr. Irving H. Leopold: In view of the discussion concerning the use of ACTH in therapy of retrolental fibroplasia, it should be noted that such therapy does have a theoretical reason for investigation. In 1942, Dr. Venning working in E. L. Browne's laboratory found that, in the first three to five days of the newborn infant's life, the infant has an extremely low supply of the adrenal cortical hormones. Even before this it had been known that the adrenal gland is not fully developed in newborn babies, but matures within a few days after birth.

Could this deficiency account for retrolental fibroplasia in prematures? If so, ACTH therapy might be helpful if it could stimulate the deficient gland to increase its secretions. Perhaps cortisone or actual cortical hormones might be more effective therapy in view of deficient glands at this time of life.

Dr. Algernon B. Reese (closing): Dr. McGavic asked why the skin hemangiomas regress. I do not know except that, in general, spontaneous regression is a characteristic of hemangiomas of infants, even full-term infants.

Dr. Scheie brought up the question of whether or not X-ray therapy injures the brain or the pituitary gland. By using small portals, and directing the rays just to the area that we seek to treat, we give tremendous doses in treating retinoblastoma, and apparently without ill effects. I do not believe that retrolental fibroplasia patients should get more than 2,500 r. I feel quite sure that this amount can be given without untoward sequelae.

I think Dr. Leopold's remarks indicate that there might be some rationale for the use of ACTH in retrolental fibroplasia.

M. Luther Kauffman,
Clerk.

CHICAGO OPHTHALMOLOGICAL SOCIETY

April 17, 1950

Dr. Derrick Vail, *president*

Clinical program

(Presented by the staff of Billings Memorial and Provident Hospitals.)

Anterior-chamber hyaline membranes

Dr. Anderson presented B. C. B., a white girl, aged nine years, first seen in the eye clinic at Billings Hospital five years ago. The complaint was a white film over the right eye since birth. The physician who delivered the child told the parents that the right eye had been injured with forceps. When the mother first saw the child there was diffuse white clouding of the entire

cornea which slowly cleared, but which seemed to become progressively worse during the next six months.

Five years ago physical examination was much the same as it now is. The left eye is normal. The nasal half of the right cornea presents a diffuse hazy appearance and scarring in the middle of substantia propria.

The underlying Descemet endothelial area has vertical irregular elevations from which arises a vertical hyaline membrane, sheet-like and shaped like a half-moon, extending obliquely through half the depth of the anterior chamber and appearing more attached to the posterior cornea at its two ends than in the middle portion. A similar smaller membrane arises from the temporal posterior cornea, as well as two or three other fine hyaline strands, all running vertically.

No keratic precipitates were present. The lens, iris, and anterior angle appeared to be normal. There were several small areas of inactive chorioretinitis in the macular area involving the fovea.

Under atropine refraction, vision was: R.E., 8/200; L.E., 20/30+3. Tension (Schiøtz) was 17 mm. Hg in each eye.

The literature lists hyaline membranes in the anterior chamber as due to: (1) Congenital, (2) birth trauma, (3) inflammatory disease (keratitis). This case is presented as one of birth injury causing rupture of the Descemet-endothelial area with added irritation.

VOGT-KOYANAGI SYNDROME

DR. J. E. CAMPBELL, JR., said that Mrs. A. A., a 52-year-old white woman, first came to the eye clinic in March, 1948, with the complaint of blurred vision of two years' duration. Vision was: R.E., 20/200; L.E., 10/200, uncorrected. Refraction disclosed that she was hyperopic and her prescription was corrected to give: R.E., 20/20; L.E., 20/100.

It was noted that she had poliosis of the left eyelashes, vitiligo areas of the skin of the left eyelids and back of the neck, a healed chorioretinal lesion in the right fundus, and a mottled appearance of the left macula.

On questioning, she stated that at the age of three years, she had a sudden onset of headache, fever, malaise, and a painful left arm. The arm, hand, and fingers were painful to movement but no paralysis was evident. This illness lasted two weeks, at which time the lashes turned white; there was a streak in the hair, and patchy areas of the skin of the back of the neck and the eyelids. She could remember no ocular pain but noted that the left eye turned in intermittently and the vision became poor. An eye doctor in Latvia, where she was then living, thought she might have leprosy, and gave her some medicine which had no effect on any of the above symptoms.

At the age of 15 years, after coming to America, she noted a sudden onset of clouding of vision to the extent that she could only see shadows for a month, after which it gradually returned to normal. There were four or five similar episodes. The last attack, at the age of 25 years, left a blurred spot in the field of vision below the fixation point.

Ocular examination revealed conjunctiva, sclera, cornea, anterior chamber, iris, and lens to be normal in each eye. There were no signs of anterior uveitis. There were a few stringy floaters in the right vitreous.

Fundus examination in the left eye showed a mottled appearance of the left macula suggesting pigmentary disturbance and possibly cystic changes and a poor foveolar reflex.

The right fundus showed an area of apparently healed old chorioretinitis, about 0.5 disc diameter in size, at the temporal margin of the disc. There were quite heavy pigment accumulations at the edge of the lesion. There was a good foveolar reflex in this eye. The papilla, vessels, and remainder of the fundi were normal in both eyes.

Cover tests revealed no manifest deviation although there was an esophoria of eight prism diopters. Tension was: L.E., 17 mm. Hg; R.E., 16 mm. Hg (Schiøtz).

Because of her complaint of "hissing and grinding" noises in both ears, she was referred to the E. N. T. clinic. There was bilateral low-tone nerve deafness and a diagnosis of Ménière's syndrome was made. Laboratory studies, including Kahn test and chest X-ray reports, revealed nothing of significance.

Although much of the assumption depends on the past history, the case is presented as possibly falling into the classification of the Vogt-Koyanagi syndrome, which is characterized by bilateral uveitis accompanied by one or more of the following: poliosis, alopecia, vitiligo, and dysacouria. The present case shows all characteristic signs except alopecia, although there is no definite evidence of involvement of the choroid of the left eye.

Exophthalmos and dysostosis craniofacialis

Dr. J. M. Richardson, Jr., presented E. T., a 47-year-old woman, who was first seen in 1933 complaining of vague symptoms which led to the diagnosis of hysteria. She was treated in the psychiatry clinic for a number of years, during which she developed personality difficulties and, in addition, an arterial hypertension. She was found to have an I.Q. of 75, with a mental age of 11 years and three months at the age of 34 years.

She was seen in the eye clinic because of complaint of headaches and burning of the eyes for 10 years. During that time the only significant finding was an error of refraction, compound hyperopic astigmatism. There was no record of exophthalmos or of fundus lesions.

In January, 1945, the patient noted protrusion of the eyes, increasing nervousness, and loss of weight. A diagnosis of Graves's disease was made and, in October, a right lobe subtotal thyroidectomy was performed. The basal metabolism rate continued to rise and in February, 1946, a left lobe thyroidectomy was done. In spite of surgery, the basal metabolism rate increased, reaching as high as plus 48 percent within a year. She was placed on thiouracil and given deep X-ray therapy to the pituitary region. There was gradual reduction in the basal metabolism rate to plus 11 percent, but the exophthalmos remained and also the emotional instability.

In April, 1948, following a blow to the right eye, there was considerable proptosis of the bulb with ecchymosis and subconjunctival hemorrhage. Commotio retinae was present and vision was reduced to light perception. A rupture of the right medial canthal ligament was found after the edema and hemorrhage had subsided, and there was secondary optic atrophy resulting in complete blindness of the eye even though X-ray films showed no evidence of fracture.

The patient had a high, relatively flat forehead, hypertelorism, exophthalmos, relatively flat malar eminences, and prognathism. It was decided to attempt a cosmetic decompression of the orbits, using a hitherto not described method with the incision in the supraorbital ridge.

The right eye was operated on on February 25, 1949, under local anesthesia, and the left eye was done one month later. The results so far as reduction of exophthalmos is concerned are equivocal, but the case is presented to demonstrate the feasibility and ease of the surgical technique used. The method, to be described later, offers numerous advantages over previously used methods.

This is the first case, so far as is known, of thyrotoxic exophthalmos occurring in a case of dysostosis craniofacialis.

Lacerations of retina

Dr. F. C. Williams said that B. N. S., a woman, aged 30 years, was first seen in the emergency room of Provident Hospital on December 15, 1948, after having sustained deep lacerations of the left side of the face, the lids, and a penetrating laceration of the left globe about 0.5 inch from the limbus, inferiorly and temporally. There was

also a small laceration over the left side of the upper lip. The right eye appeared normal: Vision of the left eye was hand movements at one foot.

The left globe was soft and the pupil was somewhat dilated and irregular in shape. Fundus reflex was present but no detail appreciated. Following emergency treatment and suture of the lacerations, the patient was hospitalized two days later.

The routine laboratory examinations were negative. She was kept in bed under conservative treatment for several days, and then was ordered to receive 50 million killed typhoid organisms in 10 cc. sterile normal saline, intravenously, as calculated by the resident and given by the interne. The interne re-calculated the dosage and administered 500 million killed typhoid organisms.

Within an hour the temperature rose to 101°F., and reached a peak of 106°F. three hours after administration, then gradually fell to 102.4°F. seven hours later.

During this episode the patient had severe chills, was nauseated, vomited several times, and complained of headache and severe abdominal pain. The blood pressure fell from 110/60 mm. Hg to 88/50 mm. Hg. The white cell count rose from 7,500 to 31,900.

She was treated during the crisis with 2,000 cc. five-percent glucose and other antipyretic measures. For the next several days she received crystalline penicillin every three or four hours, and her progress after this unpleasant episode was uneventful. The wounds healed by first intention.

Two days after fever treatment, the pupil was widely dilated, the media clearer, and the fundus perceptible. A small hemorrhagic area was noted in the inferior temporal quadrant about five to six disc diameters from the disc, but otherwise the fundus was negative.

On January 6, 1949, upon discharge from the hospital the eye appeared about the same; no retinal detachment was present. She was followed in the clinic, and there has been no flareup in the injured eye. The right eye has never shown signs of involvement. Vision on April 14, 1950, was: R.E., 20/20; L.E., 20/30. There is no evidence of retinal tear or laceration; no detachment; no floaters; and the fundi are essentially negative.

This patient is presented because, when first seen, enucleation of the injured eye was considered, because the laceration extended through the pars plana and choroid and because of the danger of sympathetic ophthalmia. Another reason for presenting the case is to emphasize the danger of typhoid-fever treatment unless carefully supervised.

Monosymptomatic glaucomatous excavation

Dr. Samuel J. Meyer said that monosymptomatic glaucomatous excavation consists solely of paleness of the optic disc with excavation, without any other anatomic changes; all functions are intact. The condition is usually acquired. It is observed only in adult and aged patients whose vascular systems are more or less defective. The affection progresses very slowly.

The excavation may remain isolated for a long time, but eventually becomes complicated by perimeter and campimeter defects, and occasionally hypertension finally appears. The accompanying symptoms indicate that the lesion of the optic nerve must be attributed to glaucoma.

There is a series of intermediary stages between the monosymptomatic excavation without ocular hypertension and complete glaucoma with ocular hypertension.

Discussion. Dr. James E. Lebensohn: Insufficient attention has been given to the relation of the capillary blood pressure of the eye to the development and course of glaucoma.

According to Bailliart, the diastolic blood pressure of the central retinal artery is 45 percent of that of the brachial artery, so that with a diastolic blood pressure of 80 mm. Hg at the brachial artery that of the central retinal artery would be around 35 mm. Hg. Although his dynamometric tech-

nique has been subject to criticism, the essential principle holds.

The spontaneous venous pulse frequently seen indicates that the pressure in the central retinal vein is in equilibrium with the intraocular pressure and hence is about 25 mm. Hg. The capillary pressure should be midway between the two or about 30 mm. Hg. If the blood pressure becomes low for any reason, capillary compression results during the diastolic phase and the circulation is thereby slowed.

Consequently, when a person whose tension is compensated receives bad news and the blood pressure suddenly falls, an acute attack of glaucoma may follow. It is the change in the relative values of intraocular pressure and capillary blood pressure that causes the circulatory and nutritional disturbances, which may be either dramatic or insidious according to circumstances.

Dr. Daniel Snydacker asked whether Dr. Meyer has correlated the facts presented with the fact that occasionally a sclerosis of the carotid artery causing severe pressure has been known to result in a glaucomatous-like atrophy of the nervehead.

Dr. Derrick Vail said that this is a lively subject which has been coming to the fore during the last five years. The matter of loss of field is more readily explainable on a vascular basis than on excavation of the nerve by pressure. The fact that one gets a nasal step, when it is the temporal part of the optic nerve that is being depressed, is paradoxical on the basis of pressure.

The study of blood supply, particularly by Wolff, has created a tremendous amount of interest. At the Eye Institute in London, work is being done to support the premise brought forward by Sir Stewart Duke-Elder recently. A paper such as this makes it necsary to re-evaluate what we have taken as a matter of course for years.

It is interesting, too, to speculate on the advantages and disadvantages of using a vasodilator drug. There are recent papers claiming improvement in the fields of vision by methods of improving the circulation. Dicumarol and nicotinic acid have been used in glaucoma simplex. McGuire presented a rather impressive paper—not so far supported by other observers—giving evidence that dicumarol associated with vasodilatation had a beneficial effect on the fields of vision.

The work of Ascher and Weinstein and others on the aqueous veins and the pressure phenomenon on the aqueous veins also is significant in directing attention to the circulatory basis of glaucoma.

Dr. Roy O. Riser asked whether Dr. Meyer would care to comment on surgery in these cases?

Dr. Peter C. Kronfeld felt that the concept presented by Dr. Meyer has certainly gained popularity in the last few years. From the papers of Sjøgren and Weekers it would appear that in their attempts to establish incomplete glaucoma these authors are not doing enough to rule out instability of ocular tension. Mention is made of tensions taken in the clinic or office. No detailed reference, however, is made to provocative tests or to determinations of ocular rigidity.

Before we accept the concept of incomplete glaucoma, every possible attempt should be made—and that is not an easy matter—to demonstrate or rule out instability of the ocular tension in those cases. It is quite possible that the concept advocated by Dr. Meyer will finally prove to be the correct one and that glaucomatous disease can be a vascular disease in different locations.

However, there can be no doubt that there is an overabundance of glaucoma in which there is close parallelism between elevation of ocular tension and progressive destruction of the optic nerve. These cases are far more numerous than the so-called incomplete glaucoma. We should not be guided too much by this very small minority of cases.

Dr. Samuel J. Meyer (closing) thanked each of the discussants. In reply to the question relative to sclerosis of the carotid artery, that syndrome is not new. Knapp described

it first in the English literature about 1932; Stöck described it earlier in the German literature.

From the few cases seen in the clinic and private practice where X-ray films were taken, only a small percentage would show sclerosis of the carotids with pressure on the optic nerve accompanied by secondary excavation and pallor of the optic disc. Most cases described in the literature have not been proven pathologically.

There must be many older people with marked sclerosis of the carotid vessels, accompanying sclerosis in the entire vascular system, with pressure on the optic nerve, who do not get the so-called excavation and pallor or atrophy of the optic disc. That must be taken into consideration.

The question as to surgery has been discussed many times at the infirmary and in private practice. For his part, he did not feel that surgery is indicated in these cases. Surgery in any case of glaucoma is not the last word; all cases go down-hill if watched long enough. This is a disease especially of older people, and one must be careful in evaluation of the individual case so far as treatment is concerned.

The question as to what constitutes normal intraocular pressure is hard to answer. It depends on the individual; it is perfectly possible that some eyes cannot tolerate so-called normal tension which is too high for that individual eye. Theoretically that is a good explanation; whether it is practical is another question.

This entity has been named "soft" glaucoma. Fortunately, it comprises only a small percentage of the glaucomatous excavations seen; most of them are accompanied by increased intraocular pressure. Whether the elevated pressure or the excavation comes first will probably be found out at some later date.

Changes in corneal curvature

Dr. Glen Floyd (by invitation) discussed the subject of changes in corneal curvature following cataract surgery.

Following extraction of senile cataract using corneoscleral sutures in 47 cases, keratometric measurements have shown rapid changes in astigmatism during the first postoperative month, and a slower but still significant change during the following three months.

A fairly uniform type of postoperative recovery curve was seen to be present in approximately 80 percent of the cases studied. Marked corneal astigmatism was present six to 10 days postoperatively and was attributed to the corneoscleral sutures. It does not portend a final large astigmatic error.

There is a slight tendency to increased final flattening of the cornea in its spherical equivalent, especially in cases in which vitreous was lost at operation.

Discussion. Dr. Peter C. Kronfeld felt that one could learn many things from Dr. Floyd's observations which constitute, he believed, the first definite demonstration of suture astigmatism. One reference is made in a paper by the "father" of this particular suture, de Mendoza, and in the Scandinavian literature there is a reference to the fear of producing suture astigmatism. Groenholm thought it advisable to place the keratoscope of Placido in front of the patient's eye while tying the suture so as not to produce too great distortion of the cornea. It is interesting to note that this suture astigmatism disappears completely and has no bearing on the outcome of the case.

We can learn from Dr. Floyd's observations that tying corneoscleral sutures of the McLean type to the point where macroscopic examination discloses no distortion or gross wrinkles is a safe procedure, although it causes a marked suture astigmatism. Clinically, Dr. Floyd has shown that postoperative astigmatism is not a great problem since, as can be seen from his graphs, the great majority of his cases at the end of three or four months showed no degree of astigmatism that interfered with visual function.

Dr. James E. Lebensohn said that, from

the clinical viewpoint, Dr. Floyd's paper indicates the value of a new type of temporary cataract lens which is now available. This lens has the bifocal-spherical element on one side and the cylinder cemented on the other side, so that the axis and power of a cylinder can be changed independently of the sphere, or new combinations made as desired until the final prescription has been determined. These temporary lenses permit patients to return to work early, since they can be changed readily as the occasion arises.

ASYMMETRY OF FACE AND EXTRAOCULAR MUSCLES

DR. J. V. CASSADY AND DR. JOHN M. THOMPSON (by invitation) presented a paper on this subject, an abstract of which follows:

Strabismus may be due to anomalies of the extraocular muscles that started during early embryologic development. Underdevelopment of the ocular muscles frequently is seen with asymmetry of the face. All of the eye muscles in one eye may be weaker than those of the other and, when asymmetry of the face also exists, the weaker muscles are on the smaller side of the face. It is probable that some strabismus believed to have been from birth injuries was from earlier developmental anomalies of the embryo.

The embryologic development of the extraocular muscles is first evident in the 24 day (10 to 14 somite) embryo and is completed by the 60-mm. embryo stage. This is the period in which the medial and lateral nasal processes are rapidly developing to form the face. Hence squint and asymmetry of the face is commonly associated either in a mild or marked degree. Hyperphoria, torticollis, distorted flattened heads, and weakness of the ocular muscles may all at times be part of the same developmental anomaly. An arrest of development either from hereditary genes or from an interference with oxygenation at a critical stage of intrauterine life may be followed by aberrant growth.

A series of cases demonstrating asymmetry of the face associated with exotropia, esotropia, and hypertrophies were presented. Measurements of the extraocular muscles of these patients in cardinal positions demonstrated a weakness of all of the extraocular muscles in one eye. This eye muscle weakness practically always was on the side of the smaller orbit and smaller side of the face.

The literature on the subject of asymmetry of the face was entirely reviewed. The smaller side of the face, the smaller orbit, and the weakness of the extraocular muscles of one eye suggest an etiologic basis for many squints which formerly were considered to be from birth injuries.

Discussion. Dr. Derrick Vail recalled a very ingenious article written a number of years ago by a photographer who had succeeded in dividing his subjects' faces into halves and printing the two sides, which showed the remarkable difference an individual would present. The photograph was cut down the middle, one side reversed and the two put together. In each picture a facial asymmetry was shown. There is nothing to this theory, but it should be easy to follow through on this method of examination. By doing what this photographer did it would thus be evident that the left side of some faces is smaller than the right side. We are grateful for the new thought interjected into this problem of intraocular motility disturbances.

Dr. J. Robert Fitzgerald mentioned other bony deformities which apparently have some relationship to strabismus, and recalled the case of a child with the bilateral retraction syndrome of Duane. She had a Klippel-Feil syndrome—absence or fusion of the cervical vertebras, congenital in orgin. There is nothing in the ophthalmic literature concerning this, but in the orthopedic literature on the Klippel-Feil syndrome there are innumerable references to the fact that such children also had a crossed eye.

Richard C. Gamble,
Secretary.

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PROFESSOR ERNST FUCHS

(June 14, 1851-November 21, 1930)

"It is difficult to think of the work done on the pathology of the eye without at the same time thinking of Prof. Ernst Fuchs . . . one of the greatest of ophthalmologists and one of the most delightful of men. Although a clinician of exceptional ability and international fame, it was as a pathologist that he justly earned his unique reputation. His whole life, indeed, was devoted to the elucidation of the morphological basis of diseases of the eyes." With this tribute Duke-Elder dedicates the section in his textbook dealing with general pathologic and therapeutic considerations.

The century that has passed since the birth of Fuchs has witnessed the climax and collapse of the political and cultural influence of Austria. When Fuchs studied in Vienna, the stars of that world-renowned medical center included Hyrtl, Brücke, Skoda, Rokitansky, Billroth, and Arlt. After graduating in 1874, Fuchs worked as Arlt's assistant in the clinic till 1880 when, at but 29 years of

age, he was called to initiate the department of ophthalmology at Liége. His remarkable insight into the fundamental problems of ophthalmology became recognized when he surpassed Wilbrand and Mules in a contest sponsored by the English Society for the Prevention of Blindness for the best treatise on the prevention of blindness. The motto chosen for identification, *Viribus Unitis* (through united strength), reflected his inclusive conception.

In 1885, Fuchs was back in Vienna to succeed Eduard Jaeger as director of the Second University Eye Clinic. Among his loyal assistants were professors of the future—Meller, Lindner, Salzmann. The medical school, then at its zenith, was staffed by Eiselberg, Weichselbaum, Lorenz, Escherich, Pirquet, Noorden, Wenckebach, Gruber, Kraus, and the Nobel Prize winners—Bárány, Landsteiner, and Wagner-Jauregg.

Memorial at grave of Ernst and Julie Fuchs. The fine black points are traces of the vines temporarily removed to take the photograph. (Courtesy of Adalbert Fuchs.)

With Fuchs, zeal for the advancement of ophthalmology was ever paramount and private practice was only of secondary concern. Among the pathologic processes elucidated in detail were sympathetic ophthalmia, endophthalmitis septica, chalazion, and pterygium. He isolated many new clinical entities including epithelial dystrophy of the cornea, keratitis disciformis, superficial punctate keratitis, dimples of the corneal limbus, episcleritis periodica fugax, retinitis circinata, and congenital inferior crescent.

But his greatest gift to ophthalmology was his textbook, first published in 1889, which ran through 12 German editions. Translations into English, Spanish, French, Italian, Russian, Chinese, and Japanese gave the work world-wide influence. Its distinguishing features were the clarity of the clinical presentation, the concise ample pathologic interpretation, and the numerous excellent original illustrations. The admirable translations by Duane, begun with the second German edition of 1892, made the treatise a favorite among the English-speaking nations. The Duane-Fuchs volume was hallowed as "the Bible of the ophthalmologist" and now, long after both men have passed, copies of any edition still command a premium.

Fuchs relinquished his formal duties at the age of 65 years to devote himself entirely to scientific interests. In the following 15 years, he produced about 100 scientific contributions, thanks to his amazing vitality, industry, genius, and organizing ability. His 40,000 histologic preparations were arranged so that complete information on any subject was immediately available. In 1929, at the age of 79 years and just a year before his sudden demise from a coronary infarct, he motored with Barkan across Europe to attend the International Congress of Ophthalmology at Amsterdam. At the close of the Congress an International Association for

the Prevention of Blindness was organized to which Fuchs was elected the first honorary member. He was honored also with the Leslie Dana Medal of the Missouri Association for the Blind, the first time the medal was awarded outside the United States.

Fuchs constantly maintained an intimate knowledge of medicine as a whole. Illustrative of his rare brilliance and versatility are his mastery of German, French, Spanish, and English; his extraordinary memory for names and faces; and his love of music, art, and nature. His hobbies were mountaineering and travel. He was well versed in botany and geology when he ascended 76 high peaks. In his tours he covered every part of the world but Australia. In 1902, he delivered the Bowman Lecture at the Ophthalmological Society of the United Kingdom. He visited America three times—in 1911 he gave the Lane Lectures in San Francisco and read a paper before the American Ophthalmological Society; in 1921-1922 he concluded a coast-to-coast lecture tour on the pathology of the eye; in 1929 he spoke at the inauguration of the Wilmer Institute and was made an honorary member of the New York Academy of Medicine. His autobiography, edited by his son Adalbert and published posthumously in 1946, contains photographs made by himself of the redwood trees in California, Old Faithful in Yellowstone, Mesa Verde, an alligator farm in Florida, the cathedral of Montreal, and Diamond Head at Honolulu.

Fuchs was the greatest ophthalmologist of his era. His influence on ophthalmology is probably second only to that of Albrecht von Graefe. He is interred in the cemetery of Kutzendorf, a village not far from Vienna, where the Hofrat was born and died. Ernst Fuchs belongs to the ages and the touching monument at his grave will ever be a shrine to the profession so deeply in his debt.

James E. Lebensohn.

THE KNAPP TESTIMONIAL FUND

The idea of a voluntarily contributed general fund to aid and advance American ophthalmology through the Section of Ophthalmology, A.M.A., is attributed to the late Dr. Eugene Bulson of Fort Wayne. Active support for his idea came from the late Dr. W. D. Posey of Philadelphia. These two well-known ophthalmologists constituted the first life trustees of the Knapp Testimonial Fund, so named in honor of the pioneer American ophthalmologist—Hermann Knapp of New York.

For 40 years the Knapp Testimonial Fund has been an active aid to American ophthalmology. How active and how effective such a fund may be depends upon the scope of the legal framework under which it operates and its financial means.

In a "stock-taking appraisal" the fund has supported the Section of Ophthalmology of the American Medical Association in divers expenses, supplied a gold medal for important contributions to the section program, has made limited contributions to national committees, given a few grants for special research, and paid for and distributed many thousand copies of the *Transactions* of the section. Some capital has been accumulated.

These activities, if of any measurable accomplishment, have been a natural sequence of the sustained loyal support given by the officers and fellows of the section. If what has been done may be called accomplishment—it has been realized within regulatory channels laid down by the founding fathers, operating through a prescribed framework established by medical organization.

In terms of the future, we need an ophthalmic organization open to all which merits the active support of our highest talents. It is an obvious truism which bears repetition that our immediate clinical fields need to be related to those of other areas in medicine, both general and special. Research in our own widespread collateral field should be integrated. In addition, our future structure

should offer stimulating meetings which encourage the younger ophthalmologists regardless of board certification. The open forum type of meeting is necessary to bring out the really new, to sustain the approved, and to enhance the prestige of ophthalmology. It can safely be said that there is much good for ophthalmology to be had from contacts with general medicine and research, and in turn, ophthalmology contributes something to these fields.

This year the joint meeting of the Section of Ophthalmology of the A.M.A. with the Association for Research is offering a compelling program. Ophthalmologists and research-minded individuals in collateral fields will profit by attending the meeting. The Knapp Testimonial Fund is happy to support this promise for the future.

No large gifts have ever been received by the fund, although long hoped for. Is it too much to hope that the wide outlook offered by our national meeting will bring added support to the Knapp Fund and to the prestige of ophthalmology? Much could be done for the science and practice of ophthalmology by a large Knapp Fund. Those who believe in a strong ophthalmic group organized on democratic lines whose meetings and programs are open to all will support this belief through contributions to the Knapp Fund.

Parker Heath.

CORRESPONDENCE

Vaccinia therapy

Editor,
American Journal of Ophthalmology:

In the March, 1951, issue of the American Journal of Ophthalmology are two articles on the treatment of vaccinia of the eye lids. Dr. King and Dr. Robie think that the aureomycin, which was given locally and parenterally, was the effective curative medium and Dr. Kline thinks that roentgen therapy was the curative factor in his patient.

In the August, 1940, issue of the *Archives of Ophthalmology*, I reported two cases of vaccinia of the eyes, both of which were entirely cured with no corneal involvement at the end of six days using sulfanilamide by mouth.

It is my impression that any antibiotic which will prevent secondary infection is efficacious in cases of vaccinia. It is to be noted that in Dr. Kline's case an antibiotic was also used. I do not believe that it makes any difference which antibiotic is administered.

(Signed) Joseph Laval,
New York, New York,

Accommodation in aphakic eyes

Editor,
American Journal of Ophthalmology:

In re-reading an article by J. W. Bettman on "Apparent accommodation in aphakic eyes," Am. J. Ophth., 33:921-928 (June) 1950, I thought it might be interesting to relate my experience with a nine-year-old girl who had had bilateral needlings for congenital cataract on at least four occasions.

This patient had been sent to a special school for handicapped children, and the question arose as to whether she should be taught Braille, because her distant corrected vision was only 20/400, better in her right eye. Her correction on first examination (glasses she wore on first visit) was found to be −6.75D. sph. in each eye with a small cylinder. On inquiry it was found that these glasses were made up through error in writing the prescription (at a large clinic), and yet the patient had worn them for over a year, and was able to read print in second-grade school textbooks at a distance of about eight inches.

On refraction, she was found to have a +6.75D. sph. to read 20/400, and was still able to read the same size print, with no addition. At a later date, this patient was re-operated by another ophthalmologist and, on

subsequent examination, vision could be improved to 20/200— with her same correction; and she was still able to read print. On this basis, Braille was not advised.

On last report, this girl is attending a special school and, at the age of 12 years, is able to read ordinary print with her distance correction and no addition. Correction is still +6.75D. sph.

I inquired about this problem, and no ophthalmologist I asked was able to give any explanation. This seems to me to be an unusual case, even more so than in the ordinary aphakic with good vision on distance correction who reads without addition, since this girl had subnormal vision for distance.

(Signed) Maurice Kadin,
Racine, Wisconsin.

Cortisone dosage

Editor,
American Journal of Ophthalmology:

Dr. Leopold and his group are to be congratulated on an excellent paper on "Cortisone in ocular disease" (Am. J. Ophth., 34: 361-371 (Mar.) 1951).

Several pertinent comments are in order.

These authors state: "Retrobulbar cortisone is not demonstratedly successful in macular degeneration and is of questionable value in posterior uveitis and retrobulbar neuritis."

Inasmuch as their dosage by the subconjunctival route was 0.05 cc. cortisone daily for three days, their statement is valid only for that dose. We have utilized subconjunctival injections of 0.20 to 0.333 cc. of pure cortone (8.5 to 12.5 mg.) in many cases of posterior uveitis with a very high incidence of successful results. We have had but few good results in macular disease and here mostly with ACTH. Apparently the larger dose utilized by us is more effective and less traumatic than three daily very small injections.

Unlike their group we have had no outright failures in syphilitic interstitial keratitis or uveitis due to Boeck's sarcoid. The relapses in the latter have been controlled. One of our most successful cases was in a woman with severe generalized Boeck's sarcoid. Her kerato-uveitis has done very well on subconjunctival cortisone. Our experience in retrobulbar neuritis have been similarly good.

Undoubtedly many of the disparities in the literature are due to the modes of usage or to the sensitivity in the individual case.

(Signed) Dan M. Gordon,
New York, New York.

BOOK REVIEWS

Worth's and Chavasse's Squint. By T. Keith Lyle. Philadelphia, The Blakiston Company, 1950. Clothbound, 319 pages, 204 figures. Price: Not listed.

The very fact that eight editions of Worth's and Chavasse's *Squint* have appeared is sufficient evidence of the value of the book. Though T. Keith Lyle has simplified the text considerably in this last edition, it still remains very difficult for the full comprehension of the average ophthalmologist. Great stress is laid on the physiology of strabismus and this is always harder to comprehend than simple rules of thumb which are not emphasized in this treatise.

Chavasse was a firm believer in the advisability of surgery. He thought that orthoptic treatment, except for total occlusion to overcome amblyopia, should primarily be utilized as an aid to diagnosis both before and after surgery. He stressed that "operative treatment should on no account be postponed because the patient is too young or too uncooperative to undergo tests to determine the exact state of his binocular function. This is to surrender a hopeful present for a doubtful future." If no progress is being made in the cure of the squint by optical and orthoptic aids, surgery should be instituted without delay.

In discussing prognosis of operations, he favors operation in infants, if necessary and

possible, to produce approximate parallelism because in infants musculo-facial contractions and palsies of convergence from disuse have not yet occurred. He advocates symmetry in surgery if possible, but unilateral operations in infancy seldom produce an asymmetrical effect. He regards the power of convergence an important clue as to the best surgical procedure.

The writer considers this book the outstanding classic in the study of squint. However, it is a mental challenge even to the advanced student of strabismus. Its primary importance is in the foundation that it lays in etiology on which the ophthalmologist can construct rational procedures.

Lawrence T. Post.

THE 1950 YEAR BOOK OF EYE, EAR, NOSE, AND THROAT. Edited by Derrick Vail, M.D., and Samuel J. Crowe, M.D. Chicago, The Year Book Publishers, 1951. 427 pages, 138 illustrations, author and subject indexes. Price: $5.00.

In its service to the organ of vision, ophthalmology has achieved many priorities. It was the first specialty to be recognized, the first to convene an international congress; and in this country, ophthalmology organized the first national society and established the first certifying board. Characteristically then, the Year Book series was inaugurated with the EENT section, and this volume marks a half century in its continuous publication.

The year 1950 also closes a decade in the common era and, in commemoration thereof, the respective editors have prefaced each section with a review of the progress made in the past years.

Vail has judiciously placed the chief emphasis on the solid achievements of these years, though not neglecting those agents which suggest promising possibilities, such as hyaluronidase, strontium 90, cortisone, and ACTH. His account of optical advances contains one of the very few misprints, the evident reference to lens coating being down as "lens casting."

The editor has carefully chosen from the world's ophthalmic literature those reports that have the greatest practical significance in diagnosis and therapy, but unfortunately modesty prevented any notice of his own publications. The articles selected are presented clearly, in adequate detail, and with all necessary illustrations. The clever juxtaposition of contributions on the same subject stresses a common or divergent viewpoint. The editorial comment, though apt, is deliberately minimal.

A cover-to-cover perusal will give the reader a delightful experience, as well as an adequate perspective of the significant advances of the year in ophthalmology.

James E. Lebensohn.

BULLETIN OF THE OPHTHALMOLOGICAL SOCIETY OF EGYPT. 1943, 1944, and 1945, volumes 36, 37, and 38.

Volume 36 (1943) contains the lecture in memory of Sayed Abdel Hamid Soliman Pasha which was delivered by R. P. Wilson, who gave an account of his own extensive observations and investigation of trachoma, a scourge which still affects 100 percent of the village population.

This lecture was followed by the reading of 38 papers on various topics, among them six papers in a symposium on myopia. The papers on trachoma, Koch-Weeks and gonococcic ophthalmia, schistosomiasis and leishmaniasis include experiences in the early years of chemotherapy.

Sabri Kamel described a new operation for pterygium, which is of frequent occurrence in Egypt. He separates the pterygium from the cornea and sclera as far back as the caruncle and cauterizes the denuded area with carbolic acid. No sutures are used.

Gamil Badir reported the occurrence of sympathetic ophthalmia in a young girl, eight days after the original accident. This is the shortest time interval between accident and

outbreak of sympathetic ophthalmia ever published. The papers, written in English, are followed by short bibliographies and summaries in Egyptian, French, and German. The excellence of the illustrations is striking.

In volume 37 (1944) is the Soliman lecture on refraction delivered by Mohammed Teweik Bey.

A symposium on corneal ulcers consisted of four papers, the most significant of which, "Trachoma carriers," was read by A. F. MacCallan, who reported on patients with few and slight signs of ocular disability, trachomatous in origin and rarely correctly diagnosed. Since such patients are capable of transmitting the disease, they should be designated as "trachoma carriers." In order to recognize trachoma at this stage, one must be able to use a slitlamp and interpret what it reveals and to understand what is pointed out by carefully stained conjunctival cells.

R. P. Wilson described Wheeler's operation for restoration of contracted sockets, a frequent occurrence in Egypt because of the many cases of severe conjunctivities with shrunken globes, prolonged and unsanitary use of glass prostheses, and severe post-trachomatous cicatrization. He also presented an interesting and very detailed case report of marginal dystrophy of the cornea which, however, does not throw any new light on the nature of this disease.

Sabri Kamel spoke on the role of the vitreous in the etiology of primary glaucoma. In his opinion, localized vitreous degeneration is the cause of "setting in motion a train of events that leads to a condition of primary glaucoma in patients with a general glaucomatous tendency." He has no facts to substantiate this hypothesis.

Papers such as those by Hassan Ali Ibrahim on an advanced case of rodent ulcer of the face and lids, illustrated in color, and by Mohammed Mokhtar on vesicular eruptions with corneal necrosis in children and retinoblastoma with extraocular extension illustrate the many difficulties encountered in the practice of medicine in Egypt.

The Soliman lecture, published in Volume 38 and delivered by Prof. M. Riad Bey, concerns some interesting aspects of comparative anatomy of the eye.

A symposium on proptosis consists of 12 well-organized discussions of various problems in diagnosis and therapy. The illustrations are excellent. These ophthalmologists have a difficult position and continuous fight in combatting widespread eye diseases among the poor and ignorant population.

Mahmoud Zaki discussed the etiology of secondary glaucoma with special emphasis on its relation to chronic dysentery, with which most Egyptians are infected.

Sabri Kamel recommends cyclodialysis in all uncontrolled cases of glaucoma simplex, secondary glaucoma following cataract extraction, and in buphthalmos.

Hana Ayoub described two cases of lymphoid hyperplasia which gave the clinical impression of tumors of the fornix.

Mohammed Mokhtar reported on vesicular eruptions on the lids with corneal necrosis in infants and children. It is a disease which may affect children in good health. No definite invader has been ascertained, and no treatment has been found to prevent the disastrous result.

A severe case of xerosis of the conjunctiva and cornea in a well-nourished 17-year-old girl was reported by Elia Nashed. Vitamin therapy, local vitamin treatment, and a diet rich in vitamins brought about very unsatisfactory results.

A notable account on the work of preventive medicine in Egypt was given by Farid Masoud. He emphasized the importance not only of protection of babies against ophthalmia and trachoma but also of general sanitation and enlightenment.

Alice R. Deutsch.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

4

PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Hirtenstein, A. **Contact lens in unilateral aphakia.** Brit. J. Ophth. **34**:668-674, Nov., 1950.

Most authors agree that the contact lens remains the most satisfactory correction for monocular aphakia. It reduces the aniseikonia and eliminates the prismatic effects of the unequal spectacles.

In this study made at Moorfields Eye Hospital during the past two years, 18 consecutive patients are described. They were 13 to 66 years of age and most of them had undergone orthoptic treatment after receiving the lens. In all but two the lens was satisfactory and had been worn for long periods of time.

Morris Kaplan.

Low, F. N. **Peripheral visual acuity.** A.M.A. Arch. Ophth. **45**:80-99, Jan., 1951.

Peripheral visual acuity has been the subject of speculation since ancient times and in the last 100 years has been measured quantitatively by numerous investigators. This paper completely surveys the present status of knowledge in this field.

R. W. Danielson.

Noronha, Mariana. **Propedeutic value of retinal after-image.** Rev. brasil. oftal. **9**:81-86, Dec., 1950.

With many drawings, the author reviews the ideas formerly advanced by Hering, Tschermak, and Bielschowsky with regard to the diagnostic value of after-image tests.

W. H. Crisp.

Renfrew, Stewart. **The regional variations of extrafoveal perception of form in the central visual fields (photopic vision). With special reference to lesions of the visual pathways.** Brit. J. Ophth. **34**:577-593, Oct., 1950.

An attempt is made to evolve a clinical method of examining and establishing the accuracy of testing form perception in central visual fields. The recorded results are comparable to the visual field chart. Special targets of squares and jumbles of varying size with comparable area were constructed. The form and light perception of patients with and without refractive error were compared and patients with intracranial lesions were examined. People with occupations requiring good peripheral vision have better than average extrafoveal perception of form. This function may respond to education. There is no close correlation be-

tween refractive error and extrafoveal form perception except when severe uncorrected refractive errors are present. It was shown that defects in the fields of form perception are a reliable guide to lesions of the visual pathways. Defects may be found in form fields before they appear in fields of light and color. Advantages of the test for form perception are that the patient has no confusion of the target and the rod supporting it, guesswork is excluded, fatigue is considerably lessened, and the complicated defect in the light field is reduced to a simpler pattern. Orwyn H. Ellis.

Sebas, S. R. **Visual recuperation (recovery of vision).** Rev. brasil. oftal. **9**:3-65, Dec., 1950.

This rather diffuse article deals with the various arguments that have appeared in the periodical literature concerning restoration of vision by means of exercises.
W. H. Crisp.

5
DIAGNOSIS AND THERAPY

Ainslie, D. **Aureomycin in opthalmology.** Brit. J. Ophth. **34**:675-680, Nov., 1950.

Aureomycin was given in drops in 0.5-percent solution, in an ointment containing 1 mg. per gram, by systemic administration of 500 to 750 mg. orally daily, and by subconjunctival injection of 3 cc. of 0.5 percent solution. Other antibiotics had been of no avail. Acute conjunctivitis, follicular conjunctivitis, chronic blepharitis, trachoma and corneal and lid ulceration following vaccination were greatly improved. In superficial punctate keratitis, dendritic keratitis and disciform keratitis there was no appreciable benefit.
Morris Kaplan.

Berens, Conrad. **A winged eye speculum.** Arch. Ophth. **43**:1080-1081, June, 1950.

The speculum has three prolongations which rest on the frontal and malar bones and on the temporal muscle, thereby holding the speculum and lids away from the eyeball and preventing pressure on the globe. John C. Long.

Donaldson, D. D. A **camera for stereoscopic photography of the anterior segment.** Arch. Ophth. **43**:1083-1087, June, 1950.

The equipment consists of two cameras facing each other and connected to their respective lenses by bellows. The lenses, in turn, face into a pair of right-angle prisms, and the other surface of each prism faces the object photographed. Special features are 1. wide range of focusing for variable magnification, 2. adjustment of the interlens distance for producing variable depth effects and 3. correction for parallax without producing distortion.
John C. Long.

Dunphy, E. B. **Ocular therapeutic principles and practical applications.** Arch. Ophth. **44**:797-812, Dec., 1950.

The use in ophthalmology of the sulfanamides, the antibiotics, the antihistaminics and the steroids of the adrenal cortex is discussed. The mode of action, therapeutic indications and side-effects of some of the outstanding drugs are described in a manner very useful to the clinician. John C. Long.

Floyd, G., and Stith, R. S. **An improved light source for the Zeiss-Nordenson fundus camera.** A.M.A. Arch. Ophth. **45**:77-79, Jan., 1951.

The camera, with this incandescent light source, has now been in use at the Illinois Eye and Ear Infirmary for several months. The results obtained in several hundred fundus photographs have been equal and, in some respects, superior to those in which the carbon arc was used.
R. W. Danielson

Gordon, D. M. **The use of ACTH and cortisone in ophthalmology.** Ophth. ibero-am. 12:114-115 (Eng.), 116-117 (Port.), 1950.

The eye department of New York Hospital-Cornell Medical Center is exploring the field of action of various hormones and steroids in ophthalmology. All possible information should be obtained before the drugs are released for general use. W. H. Crisp.

Harvey, A. McG., Howard, J. E., and Kattus, A. A. **The effect of adrenocorticotropic hormone (ACTH) and cortisone on certain diseases of the eye in which hypersensitivity plays a role.** Bull. Johns Hopkins Hosp. 87:461-481, Nov., 1950.

The results of the administration of ACTH and cortisone in two cases of nongranulomatous iritis, three of sympathetic ophthalmia, five ocular tuberculosis, one of vernal conjunctivitis, and two with uveitis following herpes zoster ophthalmicus are described. The results were beneficial in each instance. Cortisone applied locally was effective in involvement of the anterior portion of the eye. With parenteral administration there was prompt control of pericorneal congestion, clearing of the vitreous, diminution of exudates, and disappearance of retinal edema. Cortisone applied locally did not influence vitreous exudation or changes in the posterior uveal tract. (6 figures) H. C. Weinberg.

Leopold, I. H. **Clinical trial with chloramphenicol in ocular infections.** A.M.A. Arch. Ophth. 45:44-52, Jan., 1951.

Chloramphenicol solution, in a concentration of 2.5 mg. per cc. of water, has been used successfully in the local therapy of a variety of forms of conjunctivitis and dacryocystitis. Chloramphenicol systemically and locally administered was helpful in various forms of keratitis but not in uveitis. Chloramphenicol systemically administered cleared intraocular infection in three days and caused improvement in 15 patients with herpes zoster ophthalmicus. R. W. Danielson.

MacDonald, P. R. **Recent advances in ocular therapeutics.** Ophth. ibero-am. 12: 95-104 (Eng.), 105-113 (Port.), 1950.

The use in ophthalmology of antibiotic drugs of D.F.P. for glaucoma, and of the pituitary adrenocorticotropic hormones is reviewed. W. H. Crisp.

Perera, C. A. **Some practical uses of sutures in ophthalmic surgery.** New York St. J. M. 50:2438-2442, Oct. 15, 1950.

The ophthalmic surgeon may profitably consider the use of sutures for fixation, traction, and retraction. The author presents some examples employed in the removal of tumors and pterygia, in cataract surgery, and in operations for retinal separation. Uses of lid sutures, the superior rectus bridle suture, and traction sutures through or beneath the tendons of the rectus muscles are outlined in different surgical procedures. A new traction suture, tying conjunctiva to superior rectus muscle, is described for use in resection of the levator palpebrae (Blaskovic's operation). Theoretic considerations in the suturing of retroplaced and advanced rectus muscles are presented. (10 figures) H. C. Weinberg.

Rolf, D. E. **New forceps for grasping the rectus muscle.** Arch. Ophth. 43:1082, June, 1950.

This forceps has a blade at right angles to each shank so constructed that when the blades are pressed together, they slide alongside each other in a parallel manner, catching the rectus muscle between them. John C. Long.

Scoular, L. G. **Sterile anterior-chamber irrigation.** Brit. J. Ophth. 34:698-699, Nov., 1950.

A bottle which can be sterilized and used as a convenient source for saline for irrigation of the anterior chamber is briefly described and illustrated.

Morris Kaplan.

Stallard, H. B. **Appliances: operating spectacles.** Brit. J. Ophth. **34**:636-637, Oct., 1950.

The operating spectacle with a light, hinged frame provides clear, unobstructed vision of the operating field. The lenses are placed well in front of the operator's face and can be pushed quickly from the line of vision when necessary.

Orwyn H. Ellis.

Stallard, H. B. **A rack for ophthalmic needles and sutures.** Brit. J. Ophth. **34**: 637, Oct., 1950.

In this rack the threaded sutures are held firmly by three wire coils which are placed at appropriate distances and the needles and sutures are easily picked up with a needle-holder without tangling. The suture is free from lint.

Orwyn H. Ellis.

Tower, Paul. **Color photography of the eyeground.** Arch. Ophth. **43**:1074-1079, June, 1950.

A special film adapter is fitted to the Zeiss-Nordenson photographic ophthalmoscope which makes it possible to use Ektachrome film. The resulting pictures show the fundus in its entirety and are of higher fidelity than those achieved with any other technique. John C. Long.

6

OCULAR MOTILITY

Dunnington, J. H., and Regan, E. F. **Factors influencing the postoperative results in concomitant convergent strabismus.** Arch. Ophth. **44**:813-822, Dec., 1950.

Seventy-nine cases of concomitant convergent strabismus were followed for at least seven years after operation. Of these 56 percent showed a deviation of less than 10 prism diopters, 20 percent showed an outward deviation of more than 10 prism diopters and 24 percent had an inward deviation of more than 10 prism diopters. Several observations were made as to probable causes of failure. Low vision in the squinting eye seemed to increase the likelihood of postoperative divergence. The presence of 4 D. or more of hypermetropia seemed also to increase the tendency to secondary divergence. The refractive error, visual acuity and near point of convergence as well as the fixing eye and the movements of the eyes in the different directions of gaze are important preoperative considerations. The presence of abnormal retinal correspondence is not a contraindication to operation. Most poor results are produced either by injudicious selection or by postoperative adhesions.

John C. Long.

Ferraris de Gaspare, P. F. **Paralyses of external eye muscles due to chemotherapy or to antibiotics.** Boll. d'ocul. **29**:553-562, Sept., 1950.

A 44-year-old woman received 3 grams of a multisulfonamid preparation intramuscularly for three successive days for treatment of a skin disease and developed a unilateral abducens paralysis on the fourth day. The paralysis lasted six months.

A 27-year-old woman was given 6 gram polysulfonamid powder intraperitoneally during an appendectomy which was performed in local infiltration anesthesia. Three days later her right internal and right inferior recti muscles were paralyzed and remained so for at least 2 months. Other possible causes were excluded in both cases.

A 35-year-old man suffering from pleuritis sicca was given one gram of streptomycin a day, intramuscularly, for ten days, when a paralysis of the right

external rectus muscle was noticed which lasted for at least three months. Here, too, no other cause could be found. The author postulates an individual hypersensitivity to the drugs because of the small amounts administered. (References)

K. W. Ascher.

Jampolsky, Arthur. **Retinal correspondence in patients with small degree strabismus.** A.M.A. Arch. Ophth. **45**:18-26, Jan., 1951.

This is a report of a detailed examination of patients with esotropia of less than 15°. Of 84 patients, 92 percent demonstrated anomalous retinal correspondence on the major amblyoscope when the conditions of testing were adapted to the measurement of the small degree of strabismus and the small angle of anomaly. That this finding is not an artefact or conditioned to the particular method of testing is shown by comparison of the results of the same tests on normal, orthophoric patients and on patients with esophoria with and without suppression and retinal slip.

This was checked by alternative methods of examination, such as the red glass diplopia test, the Maddox test, the Tschermak congruence apparatus or the after-image test. The specific characteristics of small angle esotropia are an angle of strabismus less than 15°, which is constant and monocular, and a high incidence of anomalous retinal correspondence and anomalous peripheral fusion.

There is also a slight amblyopia of the deviating eye with the foveal or macular suppression. Such cases occur naturally, or as the result of an initial hypermetropia correction of a purely accommodative strabismus with amblyopia, or as a postoperative development following the cosmetic correction of a larger degree of esotropia. Orthoptic training usually fails in these cases. This point needs emphasis because one not infrequently finds orthoptic treatment instituted in eyes that are "almost straight," in hope of a cure, when the sensorial conditions have been misinterpreted. Ralph W. Danielson.

Johnson, L. V. **Adherence syndrome. Pseudoparalysis of the lateral or superior rectus muscles.** Arch. Ophth. **44**:870-878, Dec., 1950.

Anomalous development may result in the presence of adherence of the sheaths of the lateral rectus and inferior oblique muscles. A second form of the adherence syndrome may result from union between the superior rectus and the tendon sheath of the superior oblique. Presurgical examination with the "fixed muscle" duction test is recommended for all patients having the appearance of lateral rectus paralysis, superior rectus paralysis with overaction of the opposite inferior oblique, or superior oblique paralysis with head tilting. Methods of freeing the adhesions are described. John C. Long.

Strazzi, A. **Retinal correspondence in functional strabismus.** Boll. d'ocul. **29**: 517-526, Aug., 1950.

Sixty patients with unilateral and 20 with alternating strabismus, most of them beyond the third year of life, were studied with Bielschowsky's after-image test, the Maddox cylinder and the Herschel-Landolt double prism. In 65 percent of those with unilateral strabismus, abnormal retinal correspondence was found, more often of the disharmonious type, and more often in cases with unilateral amblyopia. Early onset of strabismus was a factor in producing abnormal retinal correspondence more frequently; so was duration of the strabismus and the angle of deviation. In the alternators, normal retinal correspondence prevailed, particularly in those younger than 11 years. Case abstracts of the alternators are given. The mechanism of suppression is discussed.

K. W. Ascher.

Strazzi, A. **The importance of amblyopia in hereditary strabismus.** Boll. d'ocul. **29**:527-536, Aug., 1950.

Two families, some members of which had esotropia and amblyopia, are discussed. In one family three members, all male, belonging to three successive generations, were affected, while among other members only occasional refractive errors occurred. In the second family a woman had esotropia and left congenital amblyopia due to a large choroidal coloboma and of her three children, two, identical twins, also had esotropia and left amblyopia. These observations led the author to a higher appreciation of amblyopia in the etiology of hereditary strabismus. K. W. Ascher.

7

CONJUNCTIVA, CORNEA, SCLERA

Agnello, F. **A case of bilateral symmetrical epitarsus.** Giorn. ital. oftal. **3**: 385-390, Sept.-Oct., 1950.

After reviewing the literature on this rare condition, the author describes the case of a girl, 11 years old, who had a bilateral, symmetrical fold of the conjunctiva of the upper tarsus attached at the upper and lower borders of the upper tarsal plates, with free edges. A probe could be passed between the fold and the tarsal conjunctiva. This condition is rare on both upper lids and symmetrically placed. Agnello believes that true cases of epitarsus are of developmental origin, while atypical cases are of inflammatory origin. V. Tabone.

Boase, A. J. **Aureomycin in trachoma.** Brit. J. Ophth. **34**:627-632, Oct., 1950.

Aureomycin used orally and locally in 36 cases of trachoma in Uganda showed remarkable improvement with short periods of treatment. Nine patients were cured. The drug produced a rapid amelioration, far better than any other medication, and much more effective than drugs of the sulfa group.

Orwyn H. Ellis.

Boyd, T. A. S., and Campbell, F. W. **Influence of ascorbic acid on the healing of corneal ulcers in man.** Brit. M. J. **2**: 1145-1148, Nov. 18, 1950.

In order to evaluate the effect of ascorbic acid on the healing of corneal wounds, the study was carried out on 51 patients. One-half of the patients received 1.5 gm. of ascorbic acid daily, the remainder were given control tablets. The administration of ascorbic acid had no significant effect upon the healing time of superficial ulcers but accelerated the healing of deep ulcers. It is suggested that there may be a localized area around the site of regenerating corneal collagen where the ascorbic acid level falls below the optimum for rapid healing. Raising the general ascorbic acid level increases the local rate of replacement and brings about accelerated healing. (3 figures, 3 tables) H. C. Weinberg.

Cavara, V. **Keratoglobus and keratoconus. A contribution to the nosological interpretation of keratoglobus.** Brit. J. Ophth. **34**:621-626, Oct., 1950.

The literature is reported and analyzed in detail. A patient with keratoglobus whose son was also seen with severe keratoconus is reported, and compared to a similar case of the literature. The author wishes to make clear the points of differential diagnosis. The term keratoglobus should be reserved for cases of bilateral ectasia with extreme enlargement and curvature of the cornea with thinning of the stroma. It is closely associated with keratoconus but should not be confused with megalocornea or with arrested hydrophthalmus.

Orwyn H. Ellis.

Das Gupta, B. K. **Streptomycin in the treatment of tuberculous ulcers of the conjunctiva.** Brit. J. Ophth. **34**:681-683, Nov., 1950.

A young man had had several large ulcers of the conjunctiva of the lids of the right eye for 2 years; both eyes and the left lids were normal. Laboratory examination gave evidence that the ulcers and similar lesions in the throat and lungs were tuberculous. The patient was given streptomycin 0.5 grams intramuscularly twice daily, and drops of 1 gram in 2 cc. of water every hour. The lesions of the lids and those elsewhere healed completely and uneventfully. (7 figures)

Morris Kaplan.

Favalora, G. **Researches and problems in trachoma. I. Histopathologic synthesis.** Riv. ital. del tracoma e di pat. ocul. esotica **1**:1-17, Jan.-March, 1949.

The author feels that the cytologic picture of trachoma is not truly characteristic of a specific disease, but is the result of a chronic inflammatory reaction of the granulating type. The persistance of the process brings about a morphologic involution of the cells present. Favalora feels that it is very important to distinguish between the nonevolutionary and the evolutionary types. The evolutionary form is essentially a chronic adhesive tarsoconjunctivitis in which the inflammatory process infiltrates the adenoid layer of the lid and stimulates the proliferation of fibrous tissue from the tarsus to the adenoid tissue. The complications, such as sclerosing of the lid, entropion and trichiasis are a direct manifestation of this process which has ended in obliteration of the adenoid layer.

Francis P. Guida.

Favalora, G. **Researches and problems in trachoma. II. Clinical synthesis on classification.** Riv. ital. del tracoma e di pat. ocul. esotica **1**:7-13, April-June, 1949.

Favalora presents his anatomicoclinical classification of trachoma.

1. Non-evolutionary or the conjunctival form (suspected cases, light forms of granulation healed with only slight scars).

2. Trachoma essentially corneal in type (rare) defined as corneal pannus, ulcerative keratitis.

3. Evolutionary or tarso-conjunctivo-corneal (frequent).

a. granulation with formation of papillae,

b. tarsitis, tarsoconjunctivitis with gelatinous changes with or without corneal complication,

c. degentrative tarsoconjunctivitis with scar formation, entropion, trichiasis with or without corneal complications,

d. miscellaneous forms which include tarso-conjunctivitis with degeneration, hyaline type, fatty degeneration, plasmacytosis, albuminoidosis and xerophthalmia.

Francis P. Guida.

Ferrata, L., Morpurgo, F., and Dugnani, E. **Experimental keratoplasty.** Giorn. ital. oftal. **3**:366-375, Sept.-Oct., 1950.

In corneal grafting on rabbits, the authors found that the nerves of the transplant began to degenerate within two weeks after operation. Reinnervation of the graft took place from the nerves of the cornea of the host, and was first apparent at the end of the second month, when the transplant usually became sensitive. Regeneration of nerves into the transplant was followed in opaque and clear grafts. Migration of newly formed vessels helped the in-growth of nerves, but was not essential.

V. Tabone.

Fine, Max. **Clearing effect of transplanted cornea on the opacity of the recipient cornea.** Arch. Ophth. **43**:1065-1073, June, 1950.

Experiments conducted on rabbits suggest that the clearing of the recipient cornea observed after successful transplantation is due, at least in part, to circulatory and metabolic changes produced by the operation itself. The failure to observe any clearing after nonpenetrating transplantations suggests that the presence of the homologous tissue alone is not the complete stimulus for such clearing, although it may play a minor part.

John C. Long.

Johnson, L. V., and Nosik, W. A. **Greater superficial petrosal neurectomy for relief of chronic bullous keratitis.** A.M.A. Arch. Ophth. **45**:32-39, Jan., 1951.

Present observations have shown that such a condition as precipitated protein membrane or vitreous in contact with the endothelium can produce edema of the cornea, and that, in certain cases at least, prevention of dilution of the salt content of the precorneal film by normal or excessive (reflex) lacrimal secretion may allow freedom from bullous keratitis. It is suggested that reflex stimulation of the greater superficial petrosal nerve from branches of the fifth cranial nerve other than the ophthalmic branch (excluding the condition of traumatic relapsing keratitis with bleb formation) or stimulation of the portio minor of the seventh nerve (nervus intermedius) could be a factor in producing microscopically or grossly recurrent erosion.

R. W. Danielson.

King, J. H., Jr. **The pterygium.** Arch. Ophth. **44**:854-869, Dec., 1950.

The surgical results in the treatment of 300 cases of pterygium are reviewed. Every pterygium should be removed surgically; and the earlier the operation is done, the better will be the functional and cosmetic result. The various surgical techniques are described and the results discussed. A surgically sound procedure is one of the "bare sclera" methods, which also calls for total removal of the diseased subconjunctival tissues. The author prefers to combine the "bare sclera" method with one that alters the direction of the conjunctival vessels, such as the Campodónico or Bangerter operation. No one technique should be used in all cases.

John C. Long.

Marsico, V. **Hypopyon keratitis in the province of Potenza.** Boll. d'ocul. **29**:537-545, Aug., 1950.

The data on 318 patients treated for serpentic ulcer between 1940 and 1949 are evaluated statistically. An improvement could be noticed in the length of hospitalization and permanent invalidity during this period. This is ascribed to improvement of social conditions, insurance and improved therapeutic agents, mainly sulfonamides and penicillin. Four tables, one of which shows the decrease of incapacity from more than 30 days in 1940, to less than 14 days in 1949, are presented.

K. W. Ascher.

Monciino, N., and Spina. P. **New investigation concerning the supposed existence of healthy carriers of inclusion bodies.** Riv. ital. del tracoma e di pat. ocul. esotica. **2**:15-18, April-June, 1950.

Microscopic studies were made of the conjunctival scrapings of 54 patients who were clinically immune to trachoma. These patients all lived in contact with trachomatous patients but never had any evidence of infection. No evidence of inclusion bodies was found. The authors concluded that they were unable to identify healthy carriers of the trachoma virus.

Francis P. Guida.

Morpurgo, F., and Ferrata, L. **Histologic observations on keratoplasty in man.** Giorn. ital. oftal. **3**:376-384, Sept.-Oct., 1950.

Reports on three cases are given. The first was a graft for an adherent leucoma, which became gradually opaque after three weeks. The eye was enucleated for painful atrophy and the graft was examined microscopically. The epithelium was regular and normal and Bowman's membrane was visible in the graft, even though it had been destroyed in the cornea of the host. The substantia propria was almost normal in the graft, while it was invaded by vessels and connective tissue in the host cornea. Descemet's membrane was wrinkled, and interrupted at the edge of the graft. In the second case, one of interstitial keratitis, the first opaque graft was removed at a second attempt at grafting. The epithelium was of irregular thickness and in places was raised by vesicles, Bowman's membrane was separated from that of the host by epithelial downgrowth. The stroma was slightly irregular, Descemet's membrane was wrinkled, but connected with that of the host by a newly formed membrane; the endothelium was partially missing and the cells were somewhat swollen. The third case was a clear graft removed after accidental death and was essentially normal with regeneration of Descemet's membrane. V. Tabone.

Oxilia, E. **Action of ultrasonic waves on the cornea of the rabbit.** Giorn. ital. oftal. **3**:350-365, Sept.-Oct., 1950.

Inaudible ultrasonic waves are those of frequency greater than 35,000 hertz (Hz) per second; they are produced by mechanical stresses on certain substances such as quartz and Rochelle salts. They produce physico-chemical changes which may have a biological action. They have been tentatively used in ophthalmology for corneal opacities and vitreous hemorrhages. The author, in experiments on enucleated rabbits' eyes, tried to assess the effect of these waves on the cornea. He found that macroscopic and microscopic changes depended on the intensity, the time of action and the distance from the source of these waves. Small exposures produced no gross changes but sections showed injury to the basal cells of the epithelium. These cells, showed abnormal staining reactions, vacuolization and coagulation of the cytoplasm, changes in the rhythm of mitosis, picnosis, karyorhexis and karyolysis. The corneal parenchyma and endothelium showed little change. Exposures for longer periods and to higher intensities produced similar changes and also detachment of the retina without a hole, cloudiness of the central part of the lens cortex, and general opacification of the cornea. The vitreous tended to become prematurely fluid. Changes were generally of a degenerative type, and those produced by slight stimulations were probably reversible, while those produced by stronger stimuli were of a permanent character.

V. Tabone.

Panepinto, V., and Lo Cascio, G. **Antistin-Privin in ocular therapeutics.** Giorn. ital. oftal. **3**:391-392, Sept., 1950.

Antistin-Privin, Ciba, was used in some allergic ocular affections, including vernal catarrh, chronic conjunctivitis and in hyperemic squamous blepharitis with good results. It is assumed that histamine-like substances are released at the site of the inflammation. The drug was found compatible with the ordinary solutions and ointments used and increased the tolerance of the conjunctiva to some irritating drugs. V. Tabone.

Pasca, G., and Latte, B. **Action of aureomycin on trachoma.** Boll. d'ocul. **29**:571-577, Sept., 1950.

Drops and ointment were used, the former instilled every two hours, the latter every four hours. Forty patients were treated, 11 with beginning trachoma, 23 in the second stage, and 6 in the third

stage with corneal pannus. In all eyes, Prowazek-Halberstaedter bodies were found and cultures were taken at regular intervals during treatment. In 10 patients one eye only was treated with aureomycin while systemic application of sulfonamids took care of the other eye. Discharge and papillary hypertrophy receded rapidly in the eyes receiving aureomycin, the nodules were more resistant to treatment. The inclusion bodies disappeared within 24 hours and the conjunctival bacteria disappeared rapidly. However the results obtained were generally no better than those obtained after penicillin or sulfonamid therapy. K. W. Ascher.

Redi, F., and Raffaele, I. **Plesiotherapy of trachoma and the behavior of the inconclusion bodies of Halberstaedter and Prowazek.** Riv. ital. del tracoma e di pat. ocul. esotica **2**:19-31, April-June, 1950.

The recent theories concerning the etiology of trachoma and the significance and classification of the inclusion bodies are reviewed. The results of studies of the behavior of the inclusion bodies in patients with first and second stage trachoma, following radio therapy, are given. It was shown that during and following the X-ray therapy, and even after the conjunctiva has shown eradication of the clinical picture of the trachoma, the inclusion bodies persist. Francis P. Guida.

Russo, A., **Aureomycin and trachoma.** Boll. d'ocul **29**:511-516, Aug., 1950.

Aureomycin ointments are well tolerated in concentrations up to 1½ percent; conjunctival and corneal manifestations of trachoma responded well to this preparation. K. W. Ascher.

Saluta, S. **Trachoma and isolation colonies for trachomatous children.** Riv. ital. del tracoma e di pat. ocul. estotica **2**:19-24, July-Sept., 1950.

The author feels that to successfully combat trachoma, diseased children should be separated from their families and placed in antitrachomatous colonies. Francis P. Guida.

Scuderi, G. **Various problems in the surgical treatment of trachoma patients. I. The canthoplasty and an operation for entropion of the lower lid.** Riv. ital. del tracoma e di pat. ocul. esotica **1**:27-35, April-June, 1949.

The author describes in detail the operative procedures used by him for enlarging the lateral canthus by separating the conjunctiva from the inner surface of the upper and lower lid at the canthus. The canthus is then enlarged and the conjunctiva is resutured to the newly formed canthus. In this way the shrinking of the canthus is avoided. The fibers of the orbicularis are transected above and below and the lateral palpebral ligament is cut in order to avoid spasm postoperatively. The method described for the treatment of entropion of the lower lid is essentially that of the H incision of Panas with these three modifications: 1. a deep intramarginal incision is made into the lid so as to allow for eversion of the lid margin, 2. a triangle of tarsus is removed in order to allow for the straightening of the tarsal plate, and 3. no sutures are placed deep in the tissue so as to minimize the effect of future scarring in the suture tract. Francis P. Guida.

Scuderi, G., and Monciino, N. **The question of trachoma in the lacrimal passages. II. Trachoma in the lacrimal canaliculi.** Riv. ital. del tracoma e di pat. ocul. esotica **2**:5-18, July-Sept., 1950.

The literature is reviewed. The lacrimal passages of 1,500 patients with trachoma were studied, and clinically three varieties are distinguishable: 1. asymptomatic, 2. cystic, and 3. nodular. Histologically the changes consisted of nonspecific granuloma, with polymorphonu-

clear cellular infiltration, and specific changes, namely, follicles in various stages of evolution and cicatrices. The authors feel that the diagnosis of true trachoma of the canaliculus can be established by biomicroscopic examination and histologic confirmation. The infection may occur either by continuity from the conjunctiva or indirectly by the tears which carry the virus into the passages. In the mild forms, probing followed by 10-percent zinc sulfate or a solution of 40-percent furacine, and in other cases irrigation with sodium penicillin solution 20,000 u/cc. every three hours for 15 days, seemed to bring about marked improvement. Francis P. Guida.

Williamson, A. D., and Leong, P. C. **Keratomalacia in Singapore and its relation to vitamin A in milk.** Med. Jour. Malaya **4**:83-95, Dec. 1949.

In Singapore, keratomalacia is most common in Chinese infants who have been fed almost exclusively on sweetened condensed milk. Fresh cans of milk gave the highest content of vitamin A.

I. E. Gaynon.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Beeson, P. B., Hankey, D. D., and Cooper, C. F., Jr. **Leptospiral iridocyclitis; evidence of human infections with leptospira pomona in the United States.** J.A.M.A. **145**:228-229, Jan. 27, 1951.

A man developed an influenza-like attack 10 days after handling raw pork and beef at work. Seven months later he developed an iridocyclitis that responded to the usual medication. The blood serum precipitation test was positive for Leptospira pomona. E. Gaynon.

Sichel, A. W., and Louw, J. G. **Sympathetic ophthalmitis of unusual onset.** Brit. J. Ophth. **34**:695-697, Nov., 1950.

This case of sympathetic ophthalmia was described in 1948 when the exciting eye was removed. The sympathizing eye was then quiescent and had a visual acuity of 6/5. During the past three years the eye remained quiet and then suddenly became red and painful with an acute iridocyclitis. Treatment consisted of enormous doses of penicillin, streptomycin, sulpha drugs and salicylates. A focus of infection in the genital system was found and eliminated. In spite of treatment, the eye was destroyed. Whether this was a renewal of the original sympathetic ophthalmia or an entirely new cyclitis could not be determined.

Morris Kaplan.

Stanworth, A. **A case of leiomyoma of the iris.** Brit. J. Ophth. **34**:633-635, Oct., 1950.

A diagnosis of leiomyoma of the iris was made preoperatively on the following facts: absence of inflammatory signs, absence of invasive characteristics, presence of hyphema, cataract localized in the area behind the mass, and absence of gross pigmentation. (1 figure, 2 photomicrographs) Orwyn H. Ellis.

Tiscornia, B. J., and Badia, J. A. **Melanosarcoma of the choroid and ciliary body.** Rev. brasil. oftal. **9**:67-80, Dec., 1950.

Two cases of melanosarcoma of the choroid, one of the ciliary body, and a fourth, under study, probably of choroidal location, are reported. The patients, all male, respectively 57, 69, 49 years old, were seen within a year, and all presented retinal detachment. W. H. Crisp.

9

GLAUCOMA AND OCULAR TENSION

Bonavolontà, Aldo. **Cyclodialysis after unsuccessful broad iridectomy and for glaucoma secondary to peripheral an-**

terior synechiae. Giorn. ital. oftal. **3**:329-349, Sept.-Oct., 1950.

In 21 cases of acute glaucoma with continued raised ocular tension in spite of a broad iridectomy, the author performed cyclodialysis in the sector of the coloboma with very good results. In 20 of the cases, there was marked lowering of tension, which persisted for one to three years; there was no further deterioration of vision or reduction of the visual fields. One case, which failed to respond to the first cyclodialysis, yielded readily to another in the lower segment of the globe. In five cases of glaucoma secondary to peripheral anterior synechia, tension was lowered and there was no further deterioration of vision. This operation is the treatment of choice in glaucoma unrelieved after a Graefe iridectomy.

V. Tabone.

Ferrer, Olga. **Results in a series of cases treated with D.F.P.** Ophth. iberoam. **12**:118-119 (Span.), 123-124 (Eng.), 1950.

Treatment of 31 glaucomatous eyes usually controlled the tension, in spite of disturbances from ciliary spasm. In one case refractory to D.F.P. (symptoms of pain from spasm, with persistent tension), tension was again controlled with pilocarpine. W. H. Crisp.

Parry, T. G. W. **Use of tantalum drains in glaucoma.** Brit. J. Ophth. **34**:684-687, Nov., 1950.

The first tantalum drain consisted of a U-shaped wire which served to replace the strip of iris in the iridencleisis operation. It was unsatisfactory because the scar tissue around it sealed off the drainage. Another drain was devised which has the form of a flattened tapering tube that is slit longitudinally. It was inserted into the anterior chamber through a keratome incision under a conjunctival flap. In 25 cases no permanent drainage was secured, but there was good control for three to four months when a more permanent operation could be done, perhaps with more safety. (7 figures.)

Morris Kaplan.

Scheie, H. G. **Goniopuncture—a new filtering operation for glaucoma.** Arch. Ophth. **44**:761-782, Dec., 1950.

Goniopuncture is a filtering operation done by carrying the tip of a knife, devised for this purpose, across the anterior chamber as in goniotomy; but, instead of sweeping the knife along the angle, a counterpuncture into the subconjunctival space is made through the trabecular region of the corneoscleral wall. When the operation is successful, a permanent fistula is established which permits subconjunctival drainage of aqueous humor. This operation has been used for the treatment of glaucoma in 16 eyes. Six had chronic simple (wide angle) glaucoma, one had glaucoma capsulare, four had juvenile glaucoma and five had congenital glaucoma. All of the eyes were characterized by having open angles. The method failed in all of the cases of chronic simple glaucoma and in the glaucoma capsulare. The tension was controlled in all of the eyes with juvenile glaucoma and in three of the five eyes with congenital glaucoma. The technique of operation and the case histories are reported in detail.

John C. Long.

Scheie, H. G. **Glaucoma. A review of the literature, 1949-1950.** Arch. Ophth. **44**: 883-908, Dec., 1950.

This is a valuable and instructive review of the important current literature on glaucoma. The mechanism of origin of primary glaucoma is discussed from the neurovascular and mechanical viewpoints. New introductions in the medical and surgical treatment of glaucoma are described. John C. Long.

10

CRYSTALLINE LENS

Alexander, H. B. **Cataract extraction with the erisophake.** California Med. **74**: 38-40, Jan., 1951.

The advantages of the erisophake over the forceps method of intracapsular extraction are: less pressure on the vitreous, less frequent rupture of the lens capsule, and better control of the lens during extraction. All types of adult cataract can be extracted. The technique recommended is described. Orwin H. Ellis.

McDonald, P. R., and Purnell, J. E. **The dislocated lens.** J.A.M.A. **145**:220-226, Jan. 27, 1951.

Dislocated lenses are congenital, traumatic or secondary to uveitis or degenerative changes in the eye. Traumatic or secondary subluxated lenses are usually associated with secondary glaucoma. Operative intervention in ectopia lentis should be limited to eyes whose vision cannot be improved by optical means. Various techniques of operative removal are discussed. I. E. Gaynon.

11

RETINA AND VITREOUS

Applebaum, Alfred. **Retrolental fibroplasia.** Ann. West. Med. and Surg. **4**:746-751, Nov., 1950.

A review of the literature to the present time is given. This disease of premature infants has been shown to cause more than half of preschool blindness. It occurs in 1.3 to 21.1 percent of children weighing under three and one-half pounds at birth. It is slightly more common in males. Vitamin E deficiency due to poor absorption of fat-soluble vitamins may be a causative factor. Clinically the first change is the development of tortuosity of the retinal vessels with marked venous distention This is followed by generalized retinal edema and grayish yellow elevations in the periphery. The vitreous becomes clouded, retinal hemorrhages and posterior synechia appear, fibrous bands form behind the lens and finally the retina becomes detached. Growth stops in the eye and the development of the bony orbit is retarded. The active phase ceases at five and one-half months of age. Histologically the essential lesion is a separation of the pars optica and the pars ciliaris retinae with proliferation of the underlying pigmented epithelium. Clinically bilateral leucocoria with shallow anterior chamber, clear lens, blue, atrophic iris and enlongated visible ciliary processes in a premature infant establish the diagnosis. Glaucoma, detached retina, posterior synechia, microphthalmia and retinal hemorrhages may also be found. The difference between this lesion and several others with similar manifestations must be recognized. Persistent hyperplastic primary vitreous is unilateral, occurs in a full-term infant and involves only the central area of the posterior lens surface. Retinal dysplasia is not associated with prematurity and is usually accompanied by severe anomalies of other organs which often cause early death. Retinoblastoma, pseudoglioma and cataract are usually unilateral and less readily confused with retrolental fibroplasia. Vitamin E has been shown to lessen the incidence in one reported series. After the condition has started, no therapy, including repeated needlings and surgical removal, is effective. Orwin H. Ellis.

Ciotola, G. **Glaucoma associated with retinosis pigmentosa.** Boll. d'ocul. **29**:489-495, Aug., 1950.

The author found 46 cases of glaucoma associated with retinosis pigmentosa in the ophthalmologic literature; among 156 patients suffering from tapetoretinal degeneration, Pagliarani (Boll. d'ocul., 1949) found only two cases of glaucoma. Between 1936 and 1948, the Rome Univer-

sity Eye Clinic took care of 165,000 ambulatory patients, 194 of whom (i.e. one-tenth of one percent) had retinosis pigmentosa, and only six of these (less than three percent) were affected by glaucoma. The case histories of these six patients are briefly reported; all had compensated ("simple") glaucoma in an advanced stage. In the series of 38 patients with glaucomatous retinosis pigmentosa reported by Gartner and Schlossmann (Am. J. Ophth., 1949), only 15 had the chronic simple type, 7 chronic congestive, 5 acute congestive, 3 absolute, and 6 undetermined. Ciotola's patients had moderately elevated eye pressure readings, and, when operated on by trephine or sclerectoiridectomy, responded well to surgery. The etiologic connection between these two eye affections is not as yet elucidated, the occurrence of glaucoma in the only eye suffering from retinosis pigmentosa (Schnabel, Arch. f. Ophth., 1878) the isolated appearence of both eye diseases in one member of an otherwise normal family, and the presence in these eyes of severe degenerative vascular lesions lead the author to the assumption of some pathogenetic relationship despite the rare occurrence of glaucoma in eyes suffering from retinosis pigmentosa.

K. W. Ascher.

Conti, O., Mussio-Fournier, J. C., Carriquiry, P., and Vanrell, F. G. **Therapeutic action of a pituitary extract in retinitis pigmentosa.** Brit. J. Ophth. **34**:655-661, Nov., 1950.

Retinitis pigmentosa is often regarded as an endocrine disorder and treatment has been based on that assumption. Results have been varied and slight. Twenty-two patients were treated by the authors with a pituitary extract from the intermediate and posterior lobes of bovine hypophyses which had no oxytocic or vasopressor effect but had an intense melanotropic action. For subcutaneous injection 400 frog units per cc. were given twice weekly in 1-cc. doses; at the same time 16,000 units per cc., isotonic with the tears, was instilled into the conjunctival sac. Instillations were preferable because of ease of application and because they were more efficient than injections. The drops were given in a series of three, spaced at 5-minute intervals. Increase in vision was noted 30 to 60 minutes after the last drop. The favorable effect lasts from 2 or 3 days to two months.

Twenty-two cases are reported in detail. In 16 there was improved visual acuity; in 4 the results were doubtful and in 2 negative. The visual acuity improved from 0.1 to 0.8 and hemeralopia improved, but there was no improvement in the visual fields. The improvement in the first case studied, his lasted for three years.

Morris Kaplan.

Gandolfi, C. **Diabetic retinopathy and capillary fragility.** Giorn. ital. oftal. **3**:321-328, Sept.-Oct., 1950.

After an extensive review of the literature of retinopathy and increased capillary fragility in diabetes, the author reports his findings in 50 diabetics without retinopathy, and in 26 with retinopathy. He found that 24 percent of those without retinopathy showed increased capillary fragility (measured by the Gothlin and Rumpell-Leede methods), while all but one of the diabetics with retinopathy had increased fragility. There was no clear evidence that hypertension, increased tension in the retinal arteries, hyperchlorinesteremia, marked hyperglycemia, or renal damage played any part in the production of the increased capillary fragility.

V. Tabone.

Keeney, A. H. **Primary pigmentary degeneration of the retina and intercurrent disseminated choroiditis.** South. M.J. **44**: 38-42, Jan., 1951.

A case of classical bilateral primary pigmentary degeneration of the retina is

reported in which the patient developed an intercurrent unilateral disseminated choroiditis of nonspecific origin.

I. E. Gaynon.

Kieth, N. M., and Wagener, H. P. **Recession of neuroretinopathy during the course of malignant hypertension: its occurrence in fifteen patients who did not receive directed therapy.** Arch. Int. Med. **87**:25-47, Jan., 1951.

Papilledema and retinopathy are frequently coexistent with malignant hypertension. Their recession without improvement of the hypertension, has often followed a program of surgical, medicinal or dietary therapy. This study, however, concerns 15 patients in whom there was subsidence of the ocular findings without any specific therapeutic procedure and in whom there was no satisfactory explanation for such improvement. The retinal picture in general conforms to this pattern: constriction of arterioles, scattered hemorrhages, cotton wool patches, then papilledema of 1 to 4 D. Not all have reduced vision. During the course of this disease functional or organic changes are usually found in the cerebrum and brain stem, heart or kidneys.

Prognosis is always difficult and serious. Usually combined failure of several vital organs is common in terminal illness. Patients with satisfactory function or with only slight insufficiency of retina, brain, heart and kidneys have the best outlook. A survival curve shows that of the 15 patients, one was alive 112 months after the first examination and that 14 died within 2 to 141 months. Recession of papilledema and retinopathy is favorable whether spontaneous or following directed therapeutic measures. At best, the serious prognostic significance of such ocular changes in hypertensive patients must be stressed. In general some 80 percent die within one year and 90 percent in two years. Claude L. LaRue.

Loewenstein, Arnold. **Intramural vessels and endothelial cells in the walls of sclerosed retinal arteries.** Brit. J. Ophth. **34**:594-600, Oct., 1950.

The author demonstrates the presence of intramural vessels in both retinal arteries and veins with numerous clear photomicrographs. The endothelial cells in sclerosed arterial walls may be empty capillaries. These studies were made on tissue from patients with hypertension, arteriosclerosis, diabetes, periarteritis nodosa and vasculitis with retinal and vitreous hemorrhages. Orwyn H. Ellis.

Muscas, M. **Correlation between pigment deposits on the posterior lens capsule and retinal detachment.** Boll. d'ocul. **29**:656-660, Oct., 1950.

Five out of 17 eyes with pigment deposits in the periphery of the posterior lens capsule showed a retinal detachment. Whether this connection has any prognostic value will be decided only if a greater number of similar cases are observed. K. W. Ascher.

Parini, F., and Musini, A. **Two new types of ocular dysgenesis; persistence and hyperplasia of the primary vitreous and retrolental fibroplasia.** Boll. d'ocul. **29**:585-602, Sept., 1950.

This seems to be the first publication on this subject in Italian. A review of American publications is given and two personal observations are described, including pathological reports. There is a discussion of the etiology and therapy. (10 photomicrographs, references)

K. W. Ascher.

Schepens, C. L. **Retinal detachment and aphakia.** A.M.A. Arch. Ophth. **45**:1-17, Jan., 1951.

An analysis of the author's cases reveals that one or several breaks were detected by direct ophthalmoscopy in 35 eyes, or 44 percent, of 79 eyes which were

carefully examined. In 26 of the 35 (74 percent) in which breaks were found with direct ophthalmoscopy additional breaks were detected with indirect ophthalmoscopy. After examination by this method, one or more breaks were found in 77 of 79 eyes, or in 97.5 percent of all eyes carefully examined. The average number of breaks for 79 eyes was 4.45 per eye. More than 80 percent of all the breaks detected were not visible with the usual methods of direct ophthalmoscopy.

During 1948 and 1949, 23 percent (88 cases) of the total number of detachments treated in the retina service of the Massachusetts Eye and Ear Infirmary occurred in aphakic patients. These cases represent a clinical entity in which the disease is probably caused by an inflammation or a degeneration in the region of the ora serrata. Detachment due to changes near the ora serata, and without any equatorial lesions, was observed in 66 percent of the patients with aphakia. The retinal breaks were multiple and extremely peripheral.

An uncomplicated cataract extraction seemed to be no more than a precipitating factor in the causation of retinal detachment. The prognosis was poorer in young aphakic patients, after loss of vitreous, after extracapsular cataract extraction and, perhaps, after discission of the intact lens. Of 69 cases, retinopexy was successful in 56.5 percent. In 55 eyes operated on by intracapsular extraction reattachment was observed in 62 percent. An excellent discussion of the paper is included. R. W. Danielson.

Sorsby, A., and Ungar, J. **Control of experimental infection of the vitreous by penicillin.** Brit. J. Ophth. **34**:645-654, Nov., 1950.

It was shown that concentration of penicillin in the vitreous after intramuscular injection of even large doses and also after application of concentrated ointments are minimal. Direct intravitreal injection gave high levels while subconjunctival or retrobulbar injection gave very satisfactory and effective concentration especially if the diluent used was adrenalin 1:1,000. In a series of rabbits the vitreous was infected with staphylococcus aureus by injecting a suspension that contained 100,000 organisms in 0.05 cc. of saline solution. Penicillin dissolved in water and in adrenalin was injected subconjunctivally or retrobulbarly immediately or after an interval of 3 to 48 hours. All the controls died of panophthalmitis after 48 hours and the treated animals reacted in different ways. One million units of penicillin was found to be too large a dose. For this reason a smaller injection of the bacteria was made and 250,000 units of penicillin were used in each injection. Here the controls died of panophthalmitis in 24 hours while those receiving penicillin in adrenalin survived and soon had normal eyes. Vitreous infections can be well controlled by subconjunctival injection of penicillin in adrenalin but speedy administration is of importance; the sooner the drug is begun the more effective it is. In man the recommended dose is one million units per injection dissolved in 1 cc. of water and 5 minims of adrenalin; this should be repeated every 24 hours until the vitreous becomes clear. Morris Kaplan.

12

OPTIC NERVE AND CHIASM

Sugar H. S., Webster, J. E. and Gurjian, E. S. **Ophthalmologic findings in spontaneous thrombosis of the carotid arteries.** Arch. Ophth. **44**:823-832, Dec., 1950.

Three cases of thrombosis of the carotid artery associated with optic atrophy are presented. In two the optic atrophy was complete and was the result of thrombosis of the central retinal artery. In the third the partial optic atrophy was ap-

parently caused by involvement of the nutrient arteries of the optic nerve. The sclerotic process affecting these vessels, together with slowing of the blood flow, produces a "spotty" involvement of the optic nerve. John C. Long.

13

NEURO-OPHTHALMOLOGY

Campbell, E. and Burkland, C. W. **Ocular manifestations of aneurysms of the circle of Willis.** New York St. J. M. **50**:2427-2432, Oct. 15, 1950.

Aneurysms of the circle of Willis are the most frequent cause of spontaneous subarachnoid hemorrhages. Involvement of adjacent nerves, oculomotor, trochlear and abducens, as well as optic and trigeminal, is quite common and is helpful in diagnostic localization. Aneurysms which impinge upon the extraocular nerves can be divided into five groups according to their location: 1. internal carotid: a. those within the cavernous sinus, b. those upon the intracranial portion of the internal carotid, and c. those occurring at the bifurcation of the carotid; 2. middle cerebral; 3. anterior cerebral and anterior communicating; 4. posterior communicating; 5. basilar and posterior cerebral.

The initial hemorrhage is fatal in approximately half the patients. The prognosis is poor because of the danger of subsequent bleeding. Many of these aneurysms are so situated that they can be surgically treated and it is wise to have arteriograms taken when possible. (8 figures.) H. C. Weinberg.

Cogan, D. G., Kubik, C. S., and Smith, W. L. **Unilateral internuclear ophthalmoplegia.** Arch. Ophth. **44**:783-796, Dec., 1950.

Eight cases of this symptom complex are presented. In every case the onset was sudden, and there was unilateral failure of internal rotation in attempted lateral conjugate gaze. Convergence was normal in four cases and could not be elicited in four. Nystagmus was present in six cases, and skew deviation in six. Postmortem examination in one case revealed a small region of infarction involving the medial longitudinal fasciculus on the side of the ophthalmoplegia. The pathologic changes in that case and the sudden onset of symptoms and associated vascular disease in most of the other cases were evidence that vascular lesions were generally responsible for unilateral internuclear ophthalmoplegia. It is suggested that whereas multiple sclerosis is the chief cause of bilateral internuclear ophthalmoplegia, vascular disease (infarction) is the usual cause of unilateral internuclear ophthalmoplegia. John C. Long.

Havener, W. H. **Cerebellar-macular abiotrophy.** A.M.A. Arch. Ophth. **45**:40-43, Jan., 1951.

A father and a daughter had degenerative disease of the nervous system. The father showed both cerebellar and macular degeneration, and because of this unusual combination the cases are presented. A rather unusual combination of hereditary degeneration of the cerebellum and of the macula is described. The two members of the family reported on exhibit the phenomenon of anticipation of heredity, illustrate the poorer prognosis of early onset and emphasize the artificiality of the age limit in differentiating Friedreich's and Marie's forms of herditary sclerosis. R. W. Danielson.

Kern, A. B. **Adie's syndrome: a benign disorder simulating tabes dorsalis.** J.A.M.A. **145**:230-231, Jan. 27, 1951.

A case of Adie's syndrome that was misdiagnosed as tabes dorsalis is presented together with a discussion of the differential diagnosis of the two diseases. I. E. Gaynon.

15

EYELIDS, LACRIMAL APPARATUS

Colombo, G. L. **Conservative treatment of chronic dacryocystitis.** Boll. d'ocul. **29**: 603-608, Sept., 1950.

By repeated instillation of strong penicillin solution (10,000 to 20,000 units per cc.) the infection in the lacrimal sac can be cured so that later probing will be less dangerous and more effective. Early disturbances of the lacrimal passages can be favorably influenced by collyria containing privine, zinc sulphate and laudanum. K. W. Ascher.

Guy, L. P. **Use of the superior rectus in operations for blepharoptosis.** New York St. J. M. **50**:2417-2420, Oct. 15, 1950.

The operations for blepharoptosis may be divided into three groups: 1. those that shorten the upper lid, 2. those that suspend the lid from the brow, and 3. those that adhere the lid to the globe and utilize the action of the superior rectus. Patients that require operation should be studied for action of the levator, oculomotor balance, jaw-winking, and phimosis of the lids. When there is action of the levator and no jaw-winking, surgical treatment by resecting the levator and tarsus is recommended. For those who have no action of the levator, the choice lies between a suspension and an adhesion operation. The author reports a case in which a Shoemaker-Kirby modification of the Motais operation was done. Amblyopia and convergence strabismus developed, and ptosis appeared two years later. The author prefers the suspension operation because complications may follow the adhesion operation. (4 figures)

H. C. Weinberg.

Obermayer, M. E., and Fox, E. T. **Superficial cutaneous inflammation in the regions of the eyes and ears.** Ann. West. Med. and Surg. **5**:583-588, Oct., 1950.

The most common cause of superficial periocular inflammation is eczema. This may be caused by sensitivity to pollens, cosmetics, antibiotics, anesthetics and other antigenic substances. Patch tests may reveal the causal agents. Neurodermatitis is of internal origin due to a hereditary allergic diathesis. Seborrheic dermatitis is a mild chronically recurring dermatosis which may occur on the eyelids. Treatment for these dermatoses is outlined, and the importance of combining local therapy with general measures including psychotherapy is emphasized.

Orwyn H. Ellis.

Sjögren, H., and Eriksen, A. **Alacrimia congenita.** Brit. J. Ophth. **34**:691-694, Nov., 1950.

Since 1884 only nine cases of congenital absence of tearing have been reported. A 5-year-old girl is described who was healthy in every way except that she had no tears, and had keratoconjunctivitis sicca. She had never had tears, but had no photophobia. Exposure to tear gas in a closed room produced no tearing but caused pain. The lacrimal gland was normal on microscopic examination and after obliteration of the lacrimal puncta the clinical signs disappeared.

Morris Kaplan.

16

TUMORS

Schlagenhauff, Kurt. **Metastatic carcinoma of the ciliary body.** Ophthalmologica **120**:229-315, Nov., 1950.

A 77-year-old man presented himself because of sudden loss of vision associated with severe pain in his right eye. A large hyphema and steaminess of the cornea concealed the deeper structures. The diagnosis of secondary glaucoma of unknown cause was made and a trephine

operation performed which was followed by several severe anterior chamber hemorrhages. Eventually the chamber contents cleared and a grayish-yellow tumor became visible in the inferonasal portion of the chamber angle. The diagnosis of metastatic tumor was made. Thorough medical examination revealed a markedly enlarged, hard, but not definitely carcinomatous prostate. The patient died of bronchopneumonia six months later. The autopsy revealed an adenocarcinoma of the prostate with very extensive metastases to the abdominal lymph glands, the bladder, the spine and the pleura. Two metastases were found in the choroid of the opposite (left) eye. The literature is reviewed. The rarity of metastatic carcinoma of the anterior uvea (31 recorded cases) is in striking contrast to the occurrence of the same tumor in the choroid. Peter C. Kronfeld.

Standal, Brynjulv. **Neurinoma of the orbit.** Acta ophth. **28**:49-70, 1950.

After a brief review of the literature on the incidence and symptomalogy of orbital neurinoma, the author reports an analysis of the case histories of this neoplasm at the Eye Department of the University of Oslo, during a ten-year period from 1939 to 1949. Among 32 primary tumors of the orbit, 9 were neurinomas. One was a neurinoma of the upper eyelid; it was highly malignant, and was removed with a good cosmetic result, and with no recurrence after a period of observation of 20 months. Two patients had malignant orbital neurinoma, which was treated by oribital exenteration. One patient died of intracranial complications nine months after the onset of the disease. The other one had no recurrence five and a half years later. The other six cases were treated with good results by excision of the tumors and postoperative X-ray irradiation. Louis Daily.

Törnquist, Ragnar. **Ophthalmic symptoms in giant follicular lymphadenopathy.** Arch. Ophth. **44**:842-853, Dec., 1950.

A case of giant follicular lymphadenopathy in a 46-year-old man is described. After having had generalized lymphadenoid enlargement for two years, lymphoid infiltrations entered the conjunctival fornices and there was invasion of the lacrimal glands and the wall of one lacrimal sac. Probably as a secondary phenomenon to the involvement of the lacrimal gland, keratoconjunctivitis sicca developed and was successfully treated by means of canalicular diathermy. Dramatic, but temporary, regression occurred after roentgen therapy and also after the intravenous injection of radioactive phosphorus. After four years of the disease, the patient is still in good condition and his body weight is almost unchanged.

John C. Long.

17

INJURIES

Dellaporta, A. **Tetanus following a perforating corneal injury.** Arch. f. Ophth. **150**:614-621, 1950.

In a boy, 11 years old, the first signs of tetanus developed 18 days after a perforating injury. During enucleation of the eye a small wooden particle emerged from the deeper parts of the eyeball. Tetanus bacilli and degenerative changes of the ciliary nerves could be demonstrated histologically. The patient recovered after local, intravenous and intraspinal injections of tetanus antitoxin.

Ernst Schmerl.

Gomer, J. J. **Corneal opacities from pure acetone.** Arch. f. Ophth. **150**:622-644, 1950.

Industrial eye injuries due to collodium acetate stimulated the author to study the causative factors. Experiments with

enucleated eyes of various kinds of animals as well as with living rabbits showed that the pathogenic substance could be identified as pure acetone, and the corneal opacities were found to be due to precipitated acetone. There was a brawny disorganization of the structure of the sclera.

Ernst Schmerl.

Marisi, F. **Follow-up of intraocular aluminum splinters.** Boll. d'ocul. **29**:661-675, Oct., 1950.

In the Rome University Eye Clinic, eight patients were observed for many years after perforating injury by one or more aluminum splinters. A table shows the age of the patients, the shape and size of the foreign bodies, their location in the injured eyes (lens, iris, anterior chamber), duration of observation 2 to 6 years), the clinical course (no complications except in one of the eyes with lens injury), and final vision (six times 10/10, once 9/10 and once 2/10 in the case of spontaneous reabsorption of the traumatic cataract). The tolerance for these foreign bodies was excellent in all cases.

K. W. Ascher.

Pelláthy, Bela. **A new method for the plastic repair of the upper lid.** Ophthalmologica **120**:349-354, Nov., 1950.

Through an injury the patient had lost most of his left upper lid plus a large piece of skin from the region of the outer canthus. The immediate repair consisted of uniting the lower lid with the stump of the upper lid. Thus the cornea and the eyeball were saved. Four months later the deformity resulting from the injury and the primary repair was corrected by moving the outer third of the lower lid into the place occupied originally by the outer half of the upper lid. The details of the operation are illustrated in photographs and diagrams. The final result was satisfactory. Peter C. Kronfeld.

Salvi, G. L. **The nature of free pseudocysts of the anterior chamber** Boll. d'ocul. **29**:578-584, Sept., 1950.

Free floating pseudocysts in the anterior chamber are a rare occurrence; three cases after perforating injury of the cornea are described. In one of them the cyst removed was found to be composed of fat which remained in the anterior chamber after penetration of penicillin ointment. K. W. Ascher.

18

SYSTEMIC DISEASE AND PARASITES

Bjork, A. **The incidence of herpes zoster, particularly herpes zoster ophthalmicus.** Acta Derm-Venereol. **30**:34-46, 1950.

The author has made a statistical study of 291 cases of herpes zoster ophthalmicus from two of the biggest eye clinics in Sweden, and, for the sake of comparison, of 233 cases of herpes zoster with different localization. This division of the cases into two groups according to the localization brings out some interesting facts. Thus, the curves show that herpes zoster (ophthalmicus excluded) is, predominantly, a disease of the young but that it is also relatively common in the old. On the other hand, herpes zoster ophthalmicus may be described a disease of old age. It is extremely rare in children. In younger people it occurs predominantly in men wheras in age it occurs more commonly in women. Theodore M. Shapira.

Heinsius, E., and Arndt, G. **Frequency, appearance and genesis of true diabetic cataract and cataract in diabetes.** Arch. f. Ophth. **150**: 555-571, 1950.

440 diabetics were studied and diabetic cataracts were observed in about 4 percent showing the following typical signs: early opacities in the posterior and anterior cortex without involvement of cap-

sule and nucleus, subcapsular formation of vacuoles and clefts, punctate, bluish gray opacities just beneath the capsule and opacities at the Y-shaped lens-sutures. 20 percent of the diabetic cataracts were combined with tuberculosis. Cataract occurred 2 or 3 times as often in diabetes as in hypertension. Endocrine factors seem to play a major role in the genesis of diabetic cataract.

Ernst Schmerl.

Magni, Sallustio. **Arachnodactyly and ectopia lentis.** Riv. oto-neuro-oftal. **25**:73-106, March-April, 1950.

The writer describes 11 cases of Marfan's syndrome in patients between 3½ and 76 years of age of whom 9 were female. Six were isolated cases and 5 were hereditary and occurred in members of two families. The Marfan syndrome is an oculoskeletal syndrome and exhibits some analogies with Marchesani's syndrome. (21 figures) Melchior Lombardo.

McKay, E. D. **Cholesterol metabolism and degenerative diseases of the eye.** Texas St.J.M. **47**:46-47, Jan., 1951.

Cholesterol is a sterol that is concerned with the metabolism of fat. An increased blood level is of diagnostic value in chronic nephrosis, diabetes, lipemia, pregnancy, cholelithiasis and hypothyroidism. Four cases are reported showing lenticular opacities, drusen and sclerosis of the vessels with an increased cholesterol blood level. I. E. Gayon.

Pagliarani, N., and Cavicchi, L. **Thyroidectomy and ocular manifestations in hyperthyroidism.** Riv. oto-neuro-oftal. **25**: 153-171, May-June, 1950.

The writers give in tabulated form the effect of thyroidectomy on the ocular symptoms in 15 patients with classical Basedow's disease or toxic adenoma of the thyroid. After the operation they noted that the palpebral symptoms regressed in the greatest percentage of the cases but an increase of the exophthalmos followed in about 50 percent. The effect on the other ocular manifestations was inconstant. The behavior of ocular symptoms after thyroidectomy in similar cases is determined by at least two elements, 1. the neurohypophyseal in the pathogenesis of the exophthalmos and 2. the thyrosympathetic in the pathogenesis of the palpebral, pupillary and other symptoms. The ophthalmologist has an important task in assisting the internist and the surgeon in the choice of the therapeutic procedure. Melchior Lombardo.

Prado, E., da Silva Lacaz, C., and de Souza, J. L. **The ocular fundi in lymphogranulomatosis venerea.** Rev. brasil. oftal. **9**:25-43, Dec., 1950.

With many references to writers who have mentioned the ocular existence of the disease, the authors review a large number of cases seen in a Brazilian clinic. The value of campimetry tests is discussed. W. H. Crisp.

Ridley, H., and Anderson, J. **A case of onchocerciasis in London and its treatment with hetrazan.** Brit. J. Ophth. **34**: 688-690, Nov., 1950.

Onchocerciasis is a disease caused by infection with the microfilaria of the threadworm, Onchocerca volulus, which enters most parts of the eye and causes corneal opacities, cataract, chorioretinal degeneration and optic atrophy. The adult worms are found in subcutaneous nodules and the infection is carried by a fly.

A man on leave from Nigeria complained of a pricking sensation in both eyes, intense photophobia and punctate corneal opacities. On examination numerous opaque plaques were seen in the superficial cornea but microfilaria were

found only after repeated studies. The new filaricidal drug hetrazen was given together with an antihistaminic, phenergan, with minimal reaction and with apparent effective eradication of the infestation and was continued for 10 weeks.

Morris Kaplan.

Rohrschneider, W. **Involvement of the eyes during active chronic tuberculosis of other organs.** Arch. f. Ophth. **150**:592-599, 1950.

The author found the eyes involved in 17 percent of 207 patients with tuberculosis of the lungs, in 14 percent of 92 patients with tuberculosis of the bones and the urogenital tract and 22 percent of 99 patients with tuberculosis of the skin. 16 percent of 200 controls showed changes of the eye ground. Contrary to former observations, the impression was gained that involvement of the eye in tuberculosis of the lungs occurs just as often as in other tuberculous conditions with a tendency to hematogenous spreading.

Ernst Schmerl.

Tóth, Zoltán. **Tetany symptoms during eye operations.** Klin. Monatsbl. f. Augenh. **117**:415-418, 1950.

Three patients with latent tetany had an attack during an intraocular operation. The possible causes that precipitated the attack and the methods of prevention are discussed.

R. Grunfeld.

Wilder, H. C. **Nematode endophthalmitis.** Tr. Am. Acad. Ophth. pp. 99-109, Nov.-Dec., 1950.

In blindness, especially of children, nematode infections are a more important factor than is generally assumed. Many cases diagnosed as pseudoglioma, Coats' disease, endophthalmitis of undetermined origin and orbital pseudotumor, are actually caused by nematode infection, which can be shown by microscopic study of serial sections. In this study of 46 enucleated eyes, principally those of children, nematode larvae or their residual hyaline capsules were observed in 24, and there were reactions sufficiently characteristic to justify a tentative diagnosis of nematode infection in the other 22. Eosinophilia of undetermined origin should be a clue for further diagnostic examination. The usual pathologic picture in nematode infection is that of an eosinophilic abscess, in some cases surrounded by epithelioid and giant cells. Later only the hyaline capsule and remains of fibrous tissue may reveal the previous infection. Because of its frequency, hookworm infection alone was studied in this contribution. Nematode infections such as strongyloides and ascares may also cause ocular disease. The patients who comprised this study lived in the central and eastern coastal states.

Chas. A. Bahn.

19

CONGENITAL DEFORMITIES, HEREDITY

Barber, A. N., and Muelling, R. J., Jr., **Cyclopia with complete separation of the neural and mesodermal elements of the eye.** Arch. Ophth. **43**:989-1003, June, 1950.

An unusual case of cyclopia, with separation of the neural and mesodermal elements of the eye, is described. The separate development of these two primitive tissues is interpreted as showing the independence of development of the mesoderm of the eye and that of the orbit. The total absence of the lens tends to confirm the hypothesis that the normal development of this structure is dependent on contact of the neural and the surface ectoderm. In the case reported the initial deviation from normal occurred during the neural plate stage, before the optic sulci were formed, and was followed by retarded development of the neural ectoderm or accelerated growth of the mesoderm or both.

John C. Long.

Leinfelder, P. J., Carroll, F. D., Falls, H. F., Cogan, D. G., and Fralick, F. B. **Symposium: Primary chorioretinal aberrations with night blindness.** Tr. Am. Acad. Ophth. pp. 607-667, July-Aug., 1950.

Leinfelder, P. J. **Classification,** pp. 607-608.

Because of the paucity of data the following classification is necessarily arbitrary. I. Congenital stationary night blindness: A. without ophthalmoscopic abnormality; B. without ophthalmoscopic but with other abnormalities; C. ophthalmoscopic appearances characterized by changes in fundus color; D. ophthalmoscopic appearances characterized by white dots in fundus. II. Delayed and progressive night blindness: A. ophthalmoscopic appearances characterized by white dots in fundus; B. ophthalmoscopic appearances characterized chiefly by retinal pigmentation, 1. without significant associated defects, 2. with associated defects a. ocular b. systemic; C. ophthalmoscopic appearances characterized by chorioretinal depigmentation, 1. gyrate atrophy type, 2. "choroideremia" type a. male form b. female carrier form.

Carroll, F. D. **Symptoms, signs and differential diagnosis,** pp. 609-616.

The symptoms and signs of stationary and progressive night blindness with and without ophthalmoscopic and other ocular and systemic defects are presented. The list includes congenital stationary and progressive night blindness, Oguchi's disease, progressive and nonprogressive retinitis punctata albescens, retinitis pigmentosa, primary and secondary, gyrate chorioretinal degeneration and choroideremia. The increased frequency in which most of these conditions are associated with ocular and extraocular degenerative processes is becoming better known. The very slight objective changes frequent in females who are carriers of these diseases but who have subjective symptoms is also of interest. Congenital night blindness is differentiated from night blindness due to deficiency of vitamin A by the nutritional and family history, the absence of the rod curve in the former and improvement following vitamin A administration in the latter condition. In the early stages of retinitis pigmentosa the presence of a ring scotoma differentiates it from somewhat similar conditions such as stationary night blindness. In secondary retinal pigment degeneration, as in lues, the pigment is usually finer textured. Progressive mental deterioration differentiates retinitis pigmentosa from constitutional macular degeneration.

Falls, H. F. **Genetics,** pp. 617-628.

With exceptional clarity the principles of modern genetics are explained with especial reference to night blindness. The inheritance patterns which occur are the complete and incomplete, the autosomal and sex linked, and the dominant and recessive. In congenital stationary night blindness the genetic pattern may be autosomal dominant or recessive, and sex-linked recessive, in Oguchi's disease, autosomal recessive, in retinitis punctata albescens, autosomal recessive, in progressive retinitis pigmentosa, complete and incomplete dominant and recessive autosomal and sex linked, in gyrate chorioretinal atrophy, autosomal recessive and incomplete sex-linked recessive. In the Lawrence-Moon syndrome one or more genes may be involved.

Cogan, D. G. **Pathology,** pp. 629-661.

Histologically there are no pathognomonic findings in retinitis pigmentosa. In reasonably advanced cases the rod and cone layer is practically absent and the outer retinal layers are much attenuated

or absent. The inner layers are relatively normal and the arteries show perivascular thickening and moderate hyalinization. Pigment migration apparently results from ameboid movement of the pigment cells through minute openings in the external limiting layer and is not directly associated with the blood vessels. This pigment may be intracellular or extracellular and frequently multiplies, as is shown by the wide variations in different types and cases.

Re-entry into the vascular circulation and its deposit in branching forms is, of course, secondary to the primary degeneration of rods and cones; Bruch's membrane and the choriocapillaris show no significant abnormalities. The optic nerve is essentially normal and the waxy color frequently observed is apparently due to slight gliosis. In the secondary form, or pseudoretinitis pigmentosa, which has many causes, the inner retinal layers are usually more disorganized than in the primary form. Among the conditions which histologically resemble retinitis pigmentosa are: congenital stationary night blindness, retinitis punctata albescens, gyrate chorioretinal atrophy, choroideremia, Oguchi's disease, chronic vitamin-A deficiency. In choroideremia the outer retinal layers are missing or thin, the pigment epithelium is absent, especially posteriorly, and the choroidal vessels are sclerosed. Histologically our conceptions of the fundus changes in vitamin-A deficiency are based only on observation of experimental animals. In some hereditary and senile macular degenerations, the histologic appearances are quite similar to those in retinitis pigmentosa. The basic abnormality is apparently metabolic and the retinal degeneration is secondary to an inability of the pigment layer and neuroepithelium to utilize vitamin A. A genetic enzymal abnormality of the ocular system is possibly the primary lesion. This outstanding contribution is based on a study of five cases observed by the author as well as numerous other cases. (41 figures)

Fralick, F. B. **Treatment and Conclusions,** pp. 662-665.

The list of therapeutic measures that have been suggested is imposing but not reassuring. The following are among the progressive degenerative, hereditary conditions which have in many cases been partially or .completely controlled by modern treatment and methods: the Schuller-Christian-Hand symdrome, diabetes, gout, pernicious anemia and familial hemolytic jaundice. The importance of early recognition and treatment is emphasized. Their incurability is frequently exaggerated because of the poor results from treatment in the late stages. The genetic status has unfortunately more limited practical application in man than in animals. The risks of cataract extraction are usually no greater in patients with retinitis pigmentosa than in those with uncomplicated senile cataract.

Duke-Elder, S. **Discussion,** pp. 666-667.

The author comments upon the difficulties in classifying primary chorioretinal aberrations with night blindness. He suggests that primary choroidal sclerosis is among the conditions which should possibly be included in this symposium. It usually appears in middle life or later, is frequently familial, and may be diffuse or local. Night blindness is an early and constant symptom and may progress to total blindness. Chas. A. Bahn.

Del Rio Cabanas, J. L. **A revision of the conception of heredity in ophthalmology.** Arch. Soc. oftal. hispano-am. **10**: 1176-1218, Nov., 1950.

The old and modern conceptions of the mechanism of heredity in various ocular

lesions are comprehensively reviewed. (45 figures) Ray K. Daily.

Mann, Ida. **The modern approach to developmental abnormalities.** Australian and New Zealand J. Surg. **20**:142-150, Aug., 1950.

In the management of developmental anomalies, we must be able to diagnose the condition, treat it if possible, assess the possible cause and be able to give advice regarding the possibility of abnormality in future members of the family. Diagnoses is dependent upon a knowledge of normal embryology. Treatment depends upon the cause. The conception that eye strain may cause further deterioration in a microöphthalmic with myopic refraction is erroneous. There is no evidence that the use of a malformed but not diseased organ can hasten its deterioration. Disease such as maternal infection or uterine hemorrhage is the only thing that can produce a congenital anomaly late in development.

I. E. Gaynon.

Salleras, A., and Ortiz de Zárate, J. C. **Recessive sex-linked inheritance of external ophthalmoplegia and myopia coincident with other dysplasis.** Brit. J. Ophth. **34**:662-667, Nov., 1950.

In the family here described 6 of 7 males had external ophthalmoplegia and myopia with other stigmata, such as absence of knee and ankle jerks, left-handedness, myelodysplasia, cardiac malformation, hernia and varices, anomalous occlusion of the teeth, goiter and thoracic malformation. All the females were ophthalmologically normal but had many of the other stigmata. There was complete bilateral ptosis, complete or almost complete bilateral ophthalmoplegia, divergent squint in three and convergent squint in the others, eccentric, dyscoric or anisocoric pupils, myopia of high degree and myopic fundus alterations. The inheritance of this gene is recessive and sex-linked, and it is possible to predict which offspring would be afflicted.

Morris Kaplan.

Spitzer, R., and Mann, I. **Congenital malformations in the teeth and eyes in mental defectives.** J. Mental Sc. **96**:681-709, July, 1950.

The evidence of developmental lens defects in patients was made a part of this study to determine whether dental malformations can be related to the pathology of endogenous mental disease since the crystalline lens, like the dental enamel, is ectodermal in origin. The 319 cases examined included idiopathic epilepsy, mongolism, and an unclassified mental deficiency. The slitlamp showed lens changes in all but 9 of the 83 patients examined. The incidence of lens changes was highest in the mongoloids, and these patients also showed the highest incidence of dental maldevelopment. The lens changes found were in the form of arcuate opacities, flake opacities of the coronary type (most common) and suture cataracts.

The dental and lenticular disorders occurred more frequently than in the normal population and were considered to be prenatal in origin. F. M. Crage.

Straub, Wolfgang. **Congenital opacities of the cornea.** Ophthalmologica **120**:401-410, Dec., 1950.

A case of congenital corneal opacity is reported in detail. The condition was bilateral and symmetrical. The opacities were located in all layers, were densest in an intermediate circular zone and relatively faint in the center. There was abundant superficial vascularization. The iris was not adherent to the cornea. These changes are taken to be the result of a primary developmental abnormality of the corneal nerves. Peter C. Kronfeld.

Vianna, Louzada. **Crouzon's disease.** Arq. brazil. de oftal. **13**:109-116, 1950.

This condition is also known as tower skull or hereditary craniofacial dysostosis. The case here reported is in a nine-year-old boy, born at term. There was exophthalmos of 19 to 22 mm. X-ray films revealed multiple synostosis of cerebral sutures. (References) W. H. Crisp.

20

HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Alvaro, M. E. **Harry Searls Gradle, 1883-1950.** Ophth. ibero-am. **12**:89-92 (Eng.), 92-94 (Port.), 1950.

This obituary notice tells, among other data, that Gradle organized the study conference conducted annually at the American Academy of Ophthalmology and Otolaryngology, became the first vice-president of the Pan-American Association of Ophthalmology in 1940, and was instrumental in having the Kellogg Foundation set aside funds for young Latin-American ophthalmologists to spend a year or two in study in the United States. W. H. Crisp.

Browne, R. C., Beck, I. F., and Saint, E. G., with the assistance of McCallum, R. I. **A comparative study of coal miners' nystagmus.** Brit. J. Ophth. **34**:601-620, Oct., 1950.

The authors believe that the most important element in coal miners' nystagmus is lack of light, rather than a neurotic disposition. A survey was made comparing the factors of the social, occupational and physical findings of miners with and without nystagmus, and what work miners with nystagmus are capable of performing. The results showed almost no difference between miners with nystagmus and a comparable group of controls. Orwyn H. Ellis.

Byrnes, Col. V. A. **Disaster strikes—what happens.** Tr. Am. Acad. Ophth. pp. 193-202, Nov.-Dec., 1950.

During the bombardment of Britain the eyes ranked fourth among serious injuries. The eyes were injured in one of every 35 casualties, and one of three of these was serious. In atomic explosions the proportions are much higher. In Hiroshima for example an estimated 100,000 were killed and another 100,000 were injured. This would mean about 4,000 cases requiring eye attention, of which 1,000 would probably be more serious, 2,000 less serious and 1,000 negligible. In Hiroshima with approximately 90,000 buildings, two of every three were destroyed in an area of nearly 5 square miles. Generalized burns were observed one and one-half miles from the explosion. The care of eye injuries is complicated by the fact that nine of every ten ophthalmologists and nurses would also be casualties and that hospitals within a range of three miles would be useless. The direct effect of the explosion, fires, falling buildings and other debris, and the lack of electricity, food, water, communication and sewer systems add other problems. In serious explosions three basic factors determine the severity, type and care of most ocular injuries. These are 1. mechanical force, 2. heat or long-wave radiations, and 3. light or short-wave radiations. In this very interesting and timely contribution the author has presented a terse and well illustrated picture of ocular involvement in devastating explosions, both atomic, such as occurred at Hiroshima, and nonatomic such as occurred at Texas City and Amboy.

Chas. A. Bahn.

Centenary of the birth of Louis Edward da Silva Araujo. Arq. brasil. de oftal. **13**:135, 1950.

A summary of the proceedings at the commemoration of this pharmaceutical pioneer of Brazil are summarized.

W. H. Crisp.

Ten Doesschate, G. **F. C. Donders' last writings.** Ophthalmologica **120**:434-436, Dec., 1950.

During the last year of his life Franciscus Cornelius Donders developed a slowly progressive left parietal lobe lesion of undetermined etiology. Some of his writings and scribblings on a scratch-pad are indicative of this disease as well as of his insight into it. He apparently used his own signature as a criterion of the state of motor control and deep sensitivity of his right arm. Between samples of his signature he described his illness as follows: "Insecurity of movements of the hand, evident from the writing. No use practicing." A few weeks later the sample signatures became illegible and shortly afterwards the end came.

Peter C. Kronfeld.

Ivy, A. C. **Medical civil defense: the background.** Tr. Am. Acad. Ophth. pp. 191-193, Nov.-Dec., 1950.

The urgent need for medical civilian defense especially against atomic bomb attack is explained. The progress which has been made in Chicago and the plan of organization are outlined. An atomic bomb explosion in the loop district, for example, would necessitate the care of an estimated 180,000 injured persons within six hours. A huge number of collecting teams would immediately move in to administer morphine, and urgent first aid and to supervise transfer to the nearest first-aid station. There are 340 of these first-aid stations, each with a personnel of 88. The more severely injured would be sent to one of the 600 casualty stations, each with a bed capacity of 300. The hospitals as far as 40 miles distant form the fourth group of units. Chas. A. Bahn.

Keeney, A. H., and Keeney, V. T. **Blindness among practicing physicians.** Arch. Ophth. **43**:1036-1055, June, 1950.

A survey has been made of the successful adjustment of physicians, historical and contemporary, to visual loss. Data from 12 blind physicians of the past and 7 currently active blind physicians are presented. The main conclusion to be drawn from this survey is that loss of vision in a physician, while imposing considerable difficulties, is not insurmountable, and that he should be encouraged to continue in medical work in spite of initial hardships. John C. Long.

Kuhn, H. S. **Emergency eye care in disaster: the layman who precedes us.** Tr. Am. Acad. Ophth. pp. 202-204, Nov.-Dec., 1950.

In atomic or other explosive disasters ocular injuries are principally 1. burns, lacerations and contusions, 2. embedded extraocular foreign matter, 3. intraocular foreign bodies. The care of the injured, as performed by advanced roving collecting teams as well as in first-aid collecting stations, casualty stations and hospitals, is discussed. For example, collecting teams would cover eyes and administer morphine if necessary. In first-aid and casualty stations cases would be routed according to their seriousness, patients with perforating eye wounds and intraocular foreign bodies by stretcher, and tagged for administration of tetanus antitoxin. Patients with burns would receive local anesthesia, hydrosulphol, and bandage. Superficial foreign bodies would be removed if possible, otherwise the patient would be sent to the rear. More complete treatment would be rendered in hospitals. Standardized military procedures, unless positively contraindicated, would be used throughout. Chas. A. Bahn.

Lancaster, W. B., and Foote, F. M. **The battle against blindness.** J.A.M.A. **145**:26, Jan. 6, 1951.

Our estimated blind population is 260,000 and 22,000 others each year have their vision reduced to 20/200. One hun-

dred twenty million dollars were spent for their care last year while some four billion were spent for tobacco and over eight billion for alcoholic beverages. Over one-fifth of our blindness is caused by infection, and there has been a remarkable decrease in ophthalmia neonatorum and syphilis. One-tenth or more is due to injury, of which half can be ascribed to occupational hazards and half to play or accidents at home. Wise legislation regulating the use of air rifles and sale of fireworks has helped among the children. Glaucoma, causing about one-eighth of our blindness, will probably increase as does our span of life. Its diagnosis and treatment are not satisfactory; they could be improved by routine tonometry. Cataracts cause about one-fifth of all blindness, some three-fourths of them being of the senile variety. By surgery useful vision might be restored to many. Among future needs for the prevention and cure of blindness is education, for which the American public is eager. The National Society for Prevention of Blindness is doing much, but it needs the help of every person interested in promoting America's eye health. Claude L. LaRue.

Medical writings of Dr. Harry Friedenwald. Arch. Ophth. **44**:879-882, Dec., 1950.

This is a complete list of the medical articles by this illustrious ophthalmologist. John C. Long.

Podestà, Hans. **Goethe's concept of the pathological colors.** Ophthalmologica **120**: 354-364, Nov., 1950.

The author reminds us that Goethe in an appendix to his "Farbenlehre" described some interesting observations pertaining to partial and total congenital colorblindness in man.

Peter C. Kronfeld.

Solares, Aniceto. **A study to improve legislation in Bolivia relative to industrial ocular accidents.** Arch. Soc. oftal. hispanoam. **10**:1083-1100, Oct., 1950.

A scale for the determination of visual disabilities in industrial injuries is presented. (3 tables) Ray K. Daily.

Sysi, R. **The development of the trachoma situation in Finland.** Acta ophth. **28**:87-95, 1950.

The data on the trachoma patients treated at the Helsinki Eye Clinic from 1926 to 1948, were analysed as to the incidence, stage of the disease, and the age of the patients. Louis Daily.

Teräskeli, H., and Oravisto, T. **The incidence of trachoma in Finland in 1948.** Acta ophth. **28**:71-85, 1950.

The data of a survey on the incidence of trachoma in Finland show that in 1948 there were 18,000 people affected with the disease. The number of trachoma patients in 1908 was 100,000 and in 1924, 70,000. The great decrease in the incidence of trachoma is attributed to social improvements, and to the general use of sulphonamides. Louis Daily.

NEWS ITEMS

Edited by DONALD J. LYLE, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received at least three months before the date of occurrence.

DEATHS

Dr. Wilhelm Buschke, Flushing, New York, died December 21, 1950, aged 43 years.

Dr. James Patrick Fitzgerald, Winnetka, Illinois, died December 25, 1950, aged 60 years.

Dr. Elmer E. Wible, Karns City, Pennsylvania, died November 20, 1950, aged 83 years.

Dr. Oscar Wilkinson, Washington, D.C., died December 16, 1950, aged 80 years.

ANNOUNCEMENTS

WAYNE POSTGRADUATE COURSE

Wayne University College of Medicine, Detroit, is accepting applications for its 1951-1952 course in basic ophthalmology beginning in September. The class meets from 8:00 a.m. to 5:00 p.m. on week days and 8:00 a.m. to 12:00 noon on Saturdays for nine months. Mornings are spent in lectures and laboratories and afternoons in the clinics of hospitals affiliated with the college of medicine. Tuition for the course is $900; the class is limited to 10 doctors. Applications should be addressed to the Postgraduate Department at the College of Medicine, 1512 St. Antoine, Detroit 26.

ORTHOPTIC EXAMINATIONS

The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in September and October, 1951.

The written examination will be nonassembled and will take place on Thursday, September 6th, in certain assigned cities and offices and will be proctored by designated ophthalmologists.

The oral and practical examination will be on Saturday, October 6th, in Chicago just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the secretary of the American Orthoptic Council, Dr. Frank D. Costenbader, 1605 22nd Street, N.W., Washington 8, D.C., and must be accompanied by the examination fee of $30. Applications will not be accepted after July 1, 1951.

MOUNT SINAI MEDICAL SEMINAR

Physicians and surgeons throughout this country and Cuba are being invited to attend the first annual medical seminar of Mount Sinai Hospital, Miami Beach, Florida. The event will be held on May 23, 24, and 25, 1951, at the Sorrento Hotel in Miami Beach.

Sponsored by the medical staff of Mount Sinai Hospital, the seminar will provide another link in the comprehensive educational research program established at this institution.

Registrations for the seminar will be limited to 200 physicians. For further information write to: Chairman, Seminar Committee, Mount Sinai Hospital, 4300 Alton Road, Miami Beach, Florida.

PHYSICIAN'S ART SHOW

The American Physicians Art Association will have an art exhibit, as usual, during the A.M.A. convention at Atlantic City. Any physician in the United States, Canada, and Hawaii desiring to participate in this show should communicate with the secretary, Dr. F. H. Redewill, 760 Market Street, San Francisco 2, California.

SOCIETIES

MEDICAL HISTORY MEETING

The American Association of the History of Medicine held its 1951 annual meeting in Baltimore, Maryland, with headquarters at the Institute of the History of Medicine of The Johns Hopkins University.

SOUTH CAROLINA SOCIETY

Officers of the South Carolina Society of Ophthalmology and Otolaryngology are: President, Dr. Murdoch Walker, Sumter; secretary-treasurer, Dr. Roderick Macdonald, Rock Hill. A joint meeting with the North Carolina Society of Ophthalmology and Otolaryngology will be held on September 10, 11, and 12, 1951, at Hendersonville, North Carolina. The headquarters will be the Skyland Hotel.

GILL HOSPITAL COURSE

At the 24th annual spring congress in ophthalmology and otolaryngology of the Gill Memorial Eye, Ear, and Throat Hospital, Roanoke, Virginia, there were 350 registrants from 38 states and all parts of Canada. The 25th, the silver anniversary congress, will be held in Roanoke from April 1 to 8, 1952.

MEXICAN SOCIETY

Officers of the Mexican Society of Ophthalmology for 1951 are: President, Dr. Abelardo Zertuche; vice-president, Dr. Daniel Silva; permanent secretary, Dr. Raul A. Chavira; annual secretary, Dr. Francisco Arensa B.; treasurer, Dr. Jorge Meyean Garcia; director of the transactions of the society, Dr. Magin Puig Solanes.

NSPB PROGRAM

The 1951 conference of the National Society for the Prevention of Blindness opened with a general assembly at which Mr. Mason H. Bigelow, president, spoke on "Let there be sight for all." Following this was a discussion on "Meeting the needs of the school child," with Dr. Charles C. Wilson, Yale University, as chairman. Other speakers were G. Wilson Younglove, Baltimore, who spoke on "Good lighting produces results"; Spencer B. Hopping, Hastings-on-Hudson, "Eye safety in the school program"; and Mrs. Dorothea di Pretoro, New York, "The partially seeing child in the regular class-room."

Dr. William L. Benedict, Rochester, Minnesota, was chairman of the conference on "Eye research: Problems and progress." The following papers were presented: "Present status of ACTH and cortisone," Dr. John M. McLean, New York; "Present status of retrolental fibroplasia," Dr. Algernon B. Reese, New York; "Relationship of fundamental research in biochemistry to clinical ophthalmology," Dr. Irving H. Leopold, Philadelphia; "Relationship of Armed Forces research to clinical ophthalmology," Dr. Henry A. Imus, Washington; "Blindness-research program of the National Institutes of Health," Dr. William H. Sebrell, Jr., Washington; and "Glaucoma research," Dr. Eugene M. Blake, New Haven, Connecticut.

"Coöperation: Industry's key to a successful vision program," was the next subject under discussion. Under the chairmanship of Dr. Leonard Greenburg, New York, these speakers were presented: Dr. Edmund B. Spaeth, Philadelphia, "The contribution of the ophthalmologist"; Reginald E. Gilmore, Washington, "The place of management"; Russell Crosby, Berwick, Pennsylvania, "Practical aspects of eye protection"; Mrs. Mary E. Delehanty, New York, "The nurse's program"; Herman Sager, O.D., Great Neck, New York, "Optometric services."

Dr. Carl E. Rice, Washington, was chairman of the section on "The government agency in prevention of blindness." Col. Victor A. Byrnes, Randolph Field, Texas, spoke on "Eye injuries in the event of an atomic attack." Dr. Ira V. Hiscock, Yale University, was chairman for the panel discussion of "Prevention of blindness through voluntary effort." Guest speaker at the conference dinner was Dr. Leonard A. Scheele, surgeon general, Public Health Service, Washington.

UNITED KINGDOM PROGRAM

At the annual meeting of the Ophthalmological Society of the United Kingdom held in London on March 29th, 30th, and 31st, the following papers were presented:

Mr. M. H. Whiting, president, "Surgical treatment of rodent ulcers near the eye"; Prof. A. Franceschetti, Dr. F. Bamatter, and Dr. John D. Blum, "Diagnostic value of ocular symptoms in juvenile chronic polyarthritis"; Mr. C. Dee Shapland, "Scleral resection: Lamellar"; Mr. J. H. Doggart, "Fisticuffs and the visual organs."

"Scleromalacia, arthritis deformans, and pemphigus," Prof. J. Francois; "Intracapsular extraction using a keratome," Mr. E. F. King; "Types of visual perseveration," Dr. Macdonald Critchley; "Malignant pigmented tumors in the neighborhood of the limbus treated by radical excision followed by corneoscleral graft: Report of three cases," Mr. Arthur Lister; "The structure of the skin of the inner side of the eyelid," Mr. Eugene Wolff.

"The life history of pigmented nevi," Mr. Charles Cook; "Some aspects of the treatment of paralysis of the extrinsic ocular muscles in exophthalmic ophthalmoplegia," Mr. T. Keith Lyle; "The influence of low atmospheric pressure on the development of the retinal blood vessels in the rat," Dr. F. W. Campbell; "Simplified procedure for combined operation for glaucoma," Dr. Thomson Henderson; "Gastric function and tobacco amblyopia," Dr. R. Leishman; "Cytoid bodies of the retina in a case of malignant disease," Dr. P. L. Kiewe and Dr. F. Dudley Hart; "Benign calcifying epithelioma of the eyelid," Dr. Norman Ashton.

On the second morning of the meeting, there was a panel discussion on "The association of ocular and articular disease." Opening speakers were Mr. L. H. Savin, Mr. A. B. Nutt, Prof. G. W. Pickering, Dr. F. Dudley Hart, and Prof. E. J. Wayne. The afternoon session was devoted to the pictorial demonstration of short cases and, at the evening meeting, films were shown.

Sir Henry Dale presented the Bowman Lecture. His subject was "The eye as a physiological reagent."

PENNSYLVANIA MEETING

The annual meeting of the Pennsylvania Academy of Ophthalmology and Otolarynology was held at the Galen Hall Hotel, Wernersville, Pennsylvania, on May 3rd, 4th, 5th, and 6th. Among the speakers who gave one-hour formal papers were:

Dr. Bernard C. Gettes, Dr. Maurice Cottle, Dr. John M. McLean, Dr. Herbert T. Kelly, Dr. Theodore Walsh, Dr. Kenneth M. Day, Dr. Raymond Carhart, Dr. Harold G. Scheie, Dr. Paul M. Moore, Dr. Francis W. Davison, Dr. Peter C. Kronfeld, Dr. Dewey Katz, Dr. Edwin B. Dunphy, and Dr. Campbell Moses.

In addition to the formal papers, 17 one-hour round-table and panel discussions were held on important subjects.

DOYNE MEMORIAL LECTURE

Mr. John Foster, Leeds, will deliver the Doyne Memorial Lecture on July 6th, at the annual Oxford Ophthalmological Congress to be held at Brasenose College, Oxford, on July 4th to 7th. The subject of Mr. Foster's address will be "Obstructions to practical ophthalmology."

WILMER RESIDENTS MEETING

At the 10th clinical meeting of the Wilmer Residents Association, held at the Wilmer Ophthalmo-

logical Institute of The Johns Hopkins Hospital and University, Baltimore, Dr. George Scott of Edinburgh, Scotland, was the guest of honor. The subject of Dr. Scott's address was "Neuromyelitis optica."

Among the other papers presented were: "An etiologic study of a series of optic neuropathies," Dr. Cecil H. Bagley; "Clinical use of ACTH and cortisone," Dr. Alan C. Woods; "ACTH and cortisone in the treatment of retrolental fibroplasia," Dr. Tullos O. Coston; "Contracture of extraocular muscles," Dr. Jack S. Guyton; "Surgical correction of strabismus fixus with ptosis," Dr. Robert C. Laughlin; "Pathology of retrolental fibroplasia," Dr. Jonas S. Friedenwald, Dr. Ella Uhler Owens, and Dr. William C. Owens.

"Utilization of the obliques with the tantalum-mesh type of implant," Dr. Angus L. MacLean; "High-speed photographic studies of ocular injury," Dr. Charles W. Tillett, Jr., and Dr. Carl Herget; "Biochemical aspects of visual processes," Dr. Gilbert Ling; "Problems of sensory innervation of eye muscles," Dr. Carlton C. Hunt; "Discharge patterns in the mammalia retina," Dr. Stephen W. Knuffler.

"Experimental results with ACTH and cortisone," Dr. Alan C. Woods and Dr. Ronald M. Wood; "Cellular and immunological reactions to intraocular tumor transplants," Dr. Albert C. Snell; "Cataracts and retinopathy in juvenile diabetes," Dr. William G. Marr; "Recent efforts in sarcoid therapy: The treatment of sarcoid uveitis with urethane," Dr. Robert Day; "Recent efforts in sarcoid therapy: The treatment of sarcoid uveitis with ACTH," Dr. Lawrence Shulman.

"Development of a vision tester for the Armed Services," Dr. Louise L. Sloan, Dr. William M. Rowland, and Miss Adelaide Altman; "Delayed clouding of corneal grafts," Dr. A. Edward Maumenee and Dr. Frank C. Winter; "Studies on the ascorbic acid of the aqueous," Dr. Bernard Becker, Dr. Erik Linnér, and Dr. Ernst Bárány; "The influence of adrenalectomy on the rate of flow of the intraocular fluid," Dr. Jonas S. Friedenwald; "Observations on the protein content of aqueous humor in rabbits receiving cortisone," Dr. S. Rodman Irvine; "A preliminary report on the antibiotic treatment of pyocyaneus infections in rabbits," Dr. Albert D. Ruedemann, Jr.

On the last morning of the conference, Dr. Alan C. Woods discussed "The treatment of uveitis"; Dr. Frank B. Walsh held a neuro-ophthalmologic clinic; Dr. Jonas S. Friedenwald, a clinical pathologic conference; Dr. Charles E. Iliff and Dr. James I. Moore, a clinic on "The use of radium in ophthalmology"; and Dr. William C. Owens discussed "Ophthalmic myology."

Personals

Dr. Samuel Jiro Kimura, instructor in ophthalmology at the University of California Medical School in San Francisco, was awarded a $30,000 five-year fellowship by the John and Mary R. Markle Foundation of New York.

Dr. Kimura was graduated from the University of California School of Medicine in 1941 and at that time entered the Army Medical Corps, serving with the famous Japanese Battalion in combat in Italy, where he won the Purple Heart. Following his certification by the American Board of Ophthalmology, Dr. Kimura was sent by the National Research Council to Nagasaki, Japan, to carry on research work in radiation cataract in the area affected by the atomic bomb.

Dr. Kimura at the present time is continuing his research work at the University of California Division of Ophthalmology.

Dr. Dan M. Gordon of New York has been appointed to the Advisory Council of the National Institute of Neurological Diseases and Blindness. Recently, Dr. Gordon addressed the Stamford (Connecticut) Medical Society on the "Use of ACTH and cortisone" and the staff of the Harlem Eye and Ear Hospital on "The nightblinding diseases."

A portrait of Dr. Alan C. Woods, professor of ophthalmology and director of the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital and University, was presented to Wilmer Institute by the Residents Association at a moving ceremony during the recent meeting of the Wilmer Residents Association. The portrait, a good likeness, shows Dr. Woods in his robes as an honorary fellow of the Royal College of Surgeons, Edinburgh.

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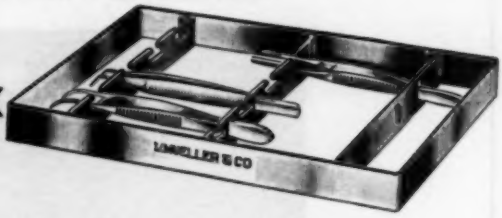

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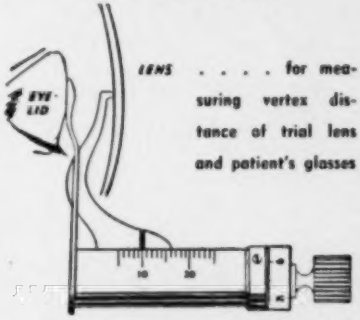

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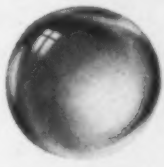

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THE PHILLIPS THYGESON

Proctor Medal Award

PROCEEDINGS

of the

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Nineteenth Meeting

San Francisco, California

June 24 and 25, 1950

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PROCEEDINGS of the ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

Nineteenth Meeting, San Francisco, California, June 24 and 25, 1950

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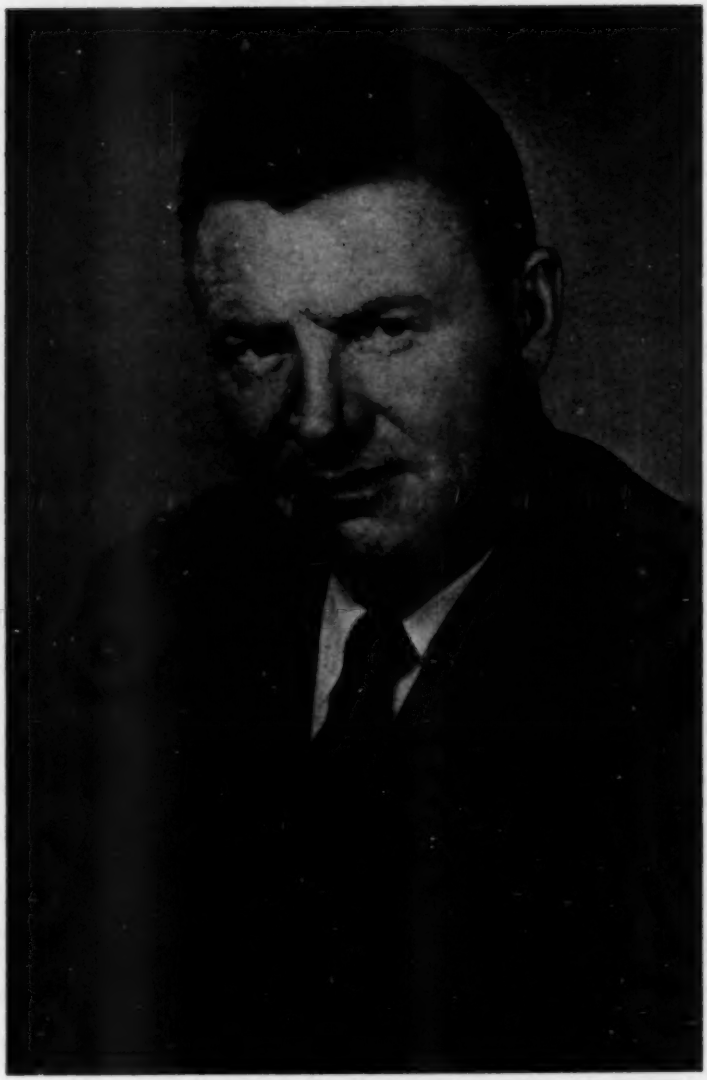

PHILLIPS THYGESON, M.D.

A SHORT BIOGRAPHY OF PHILLIPS THYGESON, M.D.

Dr. Phillips Thygeson of San Jose, California, the second distinguished American Ophthalmologist to receive the Proctor Medal Award of the Association for Research in Ophthalmology, was born at Saint Paul, Minnesota, in 1903. After his graduation from Stanford University in 1925, he studied at the Stanford University School of Medicine, receiving the degree of Doctor of Medicine in 1928. He interned at the Colorado General Hospital, Denver, and, in 1930, was awarded the degree of Doctor of Ophthalmology at the University of Colorado. Three years later, 1933, he received the degree of Master of Science (Bacteriology) from this same institution. In 1931, he became a diplomate of the American Board of Ophthalmology.

From 1930 to 1932, Dr. Thygeson was assistant in ophthalmology, University of Colorado School of Medicine; in 1932-33, National Research Council fellow, Pasteur Institute of Tunis; from 1933 to 1936, assistant professor of ophthalmology, University of Iowa College of Medicine, and from 1936 to 1945, he was associated with the College of Physicians and Surgeons, Columbia University, New York, first as assistant professor and then as professor of ophthalmology. During this period, he was also director of the Institute of Ophthalmology of the Presbyterian Hospital, New York.

After active duty in the U.S. Army from 1942 to 1946, Dr. Thygeson became a colonel in the Medical Reserve, U.S. Army, which commission he holds at the present time. From 1946 to 1948, he was section chief in ophthalmology, Branch 12, Veterans Administration.

In 1946, Dr. Thygeson became lecturer in ophthalmology at the University of California Medical School where, from 1947 to 1949, he was associate clinical professor and is now clinical professor of ophthalmology. As a special consultant, United States Public Health Service, since 1949, Dr. Thygeson has been particularly interested in studying phlyctenular keratoconjunctivitis among Alaskan natives.

Dr. Thygeson is a member of the staff of the University of California Hospital, San Francisco, and the Community Service Hospital and O'Connors Hospital, San Jose. He is an associate editor of the AMERICAN JOURNAL OF OPHTHALMOLOGY and a member of the American Board of Ophthalmology, the Santa Clara County Medical Society, the California Medical Association, the Pacific Coast Oto-Ophthalmological Society, the Association for Research in Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, the Pan-American Ophthalmological Society, the American Medical Association, the Society of American Bacteriologists, and the American Association for the Advancement of Science.

In 1938, Dr. Thygeson was awarded the Research Medal of the Section on Ophthalmology, American Medical Association, and in 1949, he received the Howe Medal of the American Ophthalmological Society for "his outstanding contributions to the field of ophthalmic bacteriology and virus diseases."

THE PROCTOR MEDAL

Funds for the establishment of the Research Medal of the Association for Research in Ophthalmology were donated in 1947 by Mrs. Francis I. Proctor of Santa Fe, New Mexico, as a memorial to her late husband. Dr. Proctor, a Boston ophthalmologist, became intensely interested in the experimental side of ophthalmology after his retirement, and participated in numerous studies on the etiology and treatment of trachoma. The purpose of the medal is to stimulate research and to honor investigators who have made notable contributions in the basic fields of ophthalmology. The medal is to be awarded without regard to the nationality or professional status of the recipient.

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* In this issue.

THE TRACHOMA-PSITTACOSIS-LYMPHOGRANULOMA VENEREUM GROUP OF VIRUSES: THE CHLAMYDOZOACEAE*

PHILLIPS THYGESON, M.D.
San Jose, California

INTRODUCTION

In 1907, Halberstaedter and Prowazek[1] discovered minute intracytoplasmic bodies, unlike any previously known disease agents, in conjunctival epithelial cells from trachoma. In 1909, similar bodies were observed independently by Stargardt[2] and Schmeichler[3] in one type of ophthalmia neonatorum now known as inclusion conjunctivitis.

There was no agreement as to the nature of these bodies and, because of the impact on the scientific world at that time of the recent discovery of the malarial plasmodia, they were originally considered to be protozoan parasites; hence the name "chlamydozoa" or "mantle bodies."

In 1906, Paschen[4] had discovered that the viruses of smallpox and vaccinia were visible in the form of minute "elementary-body" particles. The resemblance of the trachoma bodies to these variola-vaccinia bodies led to the suggestion that the trachoma and inclusion conjunctivitis bodies were in fact virus particles and responsible for the disease in which they occurred in spite of differing in important ways from the viral agents associated with the typical large virus diseases.

In 1930, Levinthal[5] and Coles,[6] working independently, discovered in the cytoplasm of reticuloendothelial cells from psittacosis the minute spherical bodies now known to be the cause of this disease, and, in 1932, Bedson and Bland[7] described a cycle of morphologic variation for these psittacosis bodies similar to that subsequently described by Thygeson[8] for the bodies of trachoma and inclusion conjunctivitis.

In 1935, Miyagawa and co-workers[9] identified similar bodies in lymphogranuloma venereum and the same life cycle of morphologic variation was demonstrated for them by Findlay and co-workers[10] and by Rake and Jones.[11]

Later, other psittacosislike viruses were isolated from the respiratory tracts of humans and animals; for example, meningopneumonitis virus (Francis and Magill[12]), spontaneous mouse pneumonitis virus (Gönnert,[13] Nigg and Eaton[14]), Australian mouse pneumonitis virus (de Burgh, *et al.*[15]), and feline pneumonitis virus (Baker[16]).

The similarity of the staining properties and developmental cycles of these agents was recognized by Bedson,[17] Thygeson,[8] and others, and helped establish the fact that there existed a distinct group of viruses which could be separated from the typical viruses just as the Rickettsiaceae, originally classified with the viruses, had ultimately been separated from them.

Bland[18] considered that the agents of the new group occupied an intermediate position between the Rickettsiaceae and the large viruses and formed a biologic link between the two life forms. He proposed grouping them with the viruses, however, as "basophilic viruses" because of the blue-staining of their inclusions and component initial bodies.

In 1945, Moshkovsky[19] proposed the family name of Chlamydozoaceae for the entire group, the genus name Miyagawanella for those infecting the reticuloendothelial system primarily, and the genus name Chlamydozoon for the agents of trachoma and inclusion conjunctivitis. The classification, with some modification, was accepted by Rake for inclusion in the 1948 revision of Bergey's *Manual of Determinative Bacteriology*.

* From the Division of Ophthalmology and the Francis I. Proctor Foundation for Research in Ophthalmology of the University of California School of Medicine.

In 1931, Coles[20] described the occurrence of rickettsialike bodies in the conjunctival scrapings from infectious or specific ophthalmia in sheep. He considered them to be the cause of the disease and to be a new species of rickettsia to which he gave the name R. conjunctivæ. Similar organisms were subsequently observed by him in a keratoconjunctivitis of domestic fowl, goats, cattle, and hogs.

He failed to find an arthropod vector for

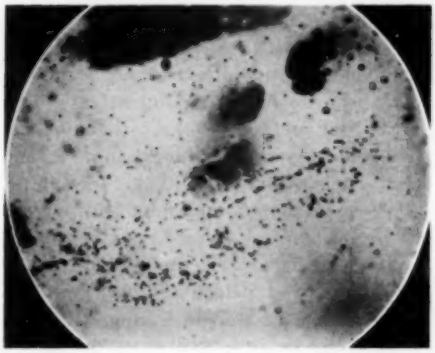

Fig. 1 (Thygeson). Elementary bodies from acute trachoma. (Giemsa stain. ×2,000.)

these organisms and this difference served to set them apart from the typical rickettsiae. He did find elementary and initial body forms, however, and a developmental cycle comparable to the cycles characteristic of members of the trachoma-psittacosis-lymphogranuloma-venereum group.

This agent has therefore been included tentatively by Moshkovsky and Rake as a member of a third genus (Colesiota) of the Chlamydozoaceae. Future studies may of course lead to a revision of this classification.

The agent of heartwater disease in sheep, usually classified with the rickettsiae and described by Cowdry[21] as Rickettsia ruminantium, has also been suggested for inclusion in the Chlamydozoaceae by virtue of its developmental cycle[22] and apparent susceptibility to sulfonamide therapy. At present, however, it is classified in Bergey's *Manual* as Cowdria ruminantium.

In addition to the scientific interest inspired by this group of viruses, great economic interest attaches to it. Trachoma is still the eye disease of greatest worldwide significance, and psittacosis, by virtue of its extraordinarily high communicability, has assumed importance in connection with biologic warfare. Lymphogranuloma venereum, while rare in the United States, is a disabling venereal disease in some parts of the world.

The members of the group of direct concern to the ophthalmologist are the viruses of lymphogranuloma venereum, inclusion conjunctivitis, and trachoma.

Family characteristics of the Chlamydozoaceae

The Chlamydozoaceae are described in Bergey's *Manual* as follows: "Small, pleomorphic, often coccoid microörganisms, usually with characteristic developmental cycle. Stain with aniline dyes. Gram negative. Behave as obligate intracytoplasmic parasites. Have not been cultivated in cell-free media."

The differentiating characteristics of the entire group which set it apart from the typical large viruses include: (1) The ease of staining of the elementary and initial bodies with ordinary histologic dyes; (2) the basophilic character of the bodies, especially of the initial bodies; (3) the character of the inclusion matrix which permits ready identification of the virus particles, in contradistinction to the acidophilic staining of the matrix of the typical large virus inclusions which tends to mask the individual virus particles; (4) the sequence of morphologic variation; and (5) the susceptibility to chemotherapy with the sulfonamides and antibiotics.

The elementary body is the basic unit (fig. 1). It is a spherical body, remarkably uniform in size and measuring about 250mμ when stained with Giemsa stain. It is nonmotile, Gram-negative, stains definitely but less intensely than bacteria with ordinary

aniline dyes, stains reddish-blue with Giemsa, and stains red or blue with the Macchiavello stain.

The initial body, first observed by Lindner[23] in trachoma, is a large swollen form of the elementary body and is seen characteristically in the first few divisions of the parasite within the cytoplasm (fig. 2). It stains bipolarly and intensely blue with Giemsa, and presents division forms. It appears to correspond to the young, swollen forms of bacteria, sometimes four or five times the normal size, which occur in the logarithmic phase of development in a new culture medium.

The developmental cycle characteristic of the group consists of an intracellular change from elementary body to initial body and, by way of transition forms, again to elementary body.

The essential difference between the members of the genus Miyagawanella and the genus Chlamydozoon lies in the tissue affinities. The viruses of the genus Miyagawanella involve primarily the tissues of the reticuloendothelial system and can be grown readily in tissue culture and on the developing chick embryo, particularly in the yolk sac; the two viruses of the genus Chlamydozoon, on the other hand, are strictly epitheliotropic and have not yet been cultivated with certainty. In morphology, particle size, and staining properties the virsues of the two genera are all very much alike.

The special characteristics of the genus Colesiota, whose classification as a member of the Chlamydozoaceae is still open to question, will be discussed in a final section of this review.

The important properties of the Chlamydozaceae are compared in Table 1.

Lymphogranuloma-venereum virus (M. lymphogranulomatis)

Lymphogranuloma venereum is of special interest as the latest venereal disease to be described and as a protean infection with rare but important eye complications. There is reason to believe that it has existed at least since the time of John Hunter who described inguinal buboes which were in all probability manifestations of it. It was not until 1913, however, that Durand, Nicolas, and Favre[24] identified the various lesions of the disease as pertaining to one clinical entity. They called it "subacute inguinal lymphogranulomatosis," described its sexual transmission, and differentiated it from syphilis and tuberculosis.

In 1925, Frei[25] developed an allergic skin

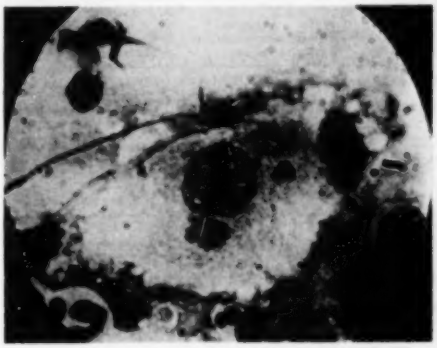

Fig. 2 (Thygeson). Inclusion body of trachoma showing initial body forms. (Giemsa stain. ×1,750.)

test for the disease, now known as the Frei test, in which heat-sterilized bubo pus, injected intradermally, elicited a tuberculinlike reaction in affected individuals.

In 1930, Hellerström and Wassén[26] succeeded in transmitting the disease to monkeys by intracerebral inoculation, and Levaditi and co-workers[27] (1932) and Findlay[28] (1933) proved that all its diverse manifestations were caused by one virus.

Levaditi and co-workers[27] (1932) established the susceptibility of the mouse to the disease and demonstrated the development of virucidal antibodies after infection. In 1935, Miyagawa and co-workers[9] showed that the virus could be seen in the form of elementary bodies, and Findlay and co-workers[10] (1938) and Rake and Jones[11] (1942)

showed that the elementary bodies were derived from larger initial body forms in a cycle of development like that of the other viruses in this group.

Rake, McKee, and Shaffer[29] (1940) showed the affinity of the virus for the yolk sac of the developing chick embryo and elaborated a complement-fixation test and an improved skin test for diagnosis.

The primary lesion develops within a few days after exposure as an herpetiform vesicle, usually on the glans or prepuce of the penis or on the labia. When the vesicle bursts it leaves a shallow, grayish ulcer which is evanescent and heals without cicatrization.

Enlargement of the regional lymph nodes occurs in from 7 to 14 days after appearance of the initial lesion, and in about half the cases the nodes become necrotic and drain. The infection often spreads to the anorectal region, particularly in the female.

Chronic inflammatory lesions develop which may produce such manifestations as elephantiasis of the labia and other soft parts in the female, a condition known as esthiomene. The rectal type may lead to stricture

TABLE 1

PROPERTIES OF THE CHLAMYDOZOACEAE

	C. Trachomatis	C. Oculogenitale	M. Lymphogranulomatis	M. Psittaci	C. Conjunctivae
Morphology	Elementary Body-Initial Body Variation	Elementary Body-Initial Body Variation	Elementary Body-Initial Body Variation	Elementary Body-Initial Body Variation	Inconstant Elementary Body-Initial Body Variation
Staining Properties Gram	Negative	Negative	Negative	Negative	Negative
Giemsa	Purplish red to blue	Purplish red to blue	Purplish red to blue	Purplish red to blue	Purplish red to blue
Iodine	Matrix stains	Matrix stains	Does not stain	Does not stain	Does not stain
Filtrability	Filters with great difficulty	+	+	+	+
Tissue tropism	Epithelium of conjunctiva, cornea, and lacrimal sac	Epithelium of conjunctiva, urethra, and cervix	Prefers cells of mesodermal origin	Prefers cells of mesodermal origin	Conjunctival and corneal epithelium
Cultivability	Not cultivated with certainty	Not cultivated with certainty	Tissue culture; chorioallantoic membrane and yolk sac	Tissue culture; chorioallantoic membrane, yolk sac, and allantoic sac	Not cultivated
Immunology: Complement fixation	Common antigen with group	Common antigen with group	Common antigen with group	Common antigen with group	Not known
Frei test	Negative	Negative	Positive	Negative	Not known
Immunity	No permanent immunity	No permanent immunity	Immunity associated with persistence of virus	Immunity associated with persistence of virus	Not known
Infectivity	Low	Low. Eye to eye transmission rare	Low. Extragenital infections rare	Extremely infectious	High infectivity in herds and flocks
Epidemiology	Eye to eye transmission	Genito-urinary tract to eye	Venereal transmission	Airborne	Not known
Toxin production	Not demonstrated	Not demonstrated	+	+	Not known
Leukocytic reaction	Neutrophilic	Neutrophilic	Neutrophilic	Not characteristic	Neutrophilic
Susceptible experimental animals	Monkeys and apes	Monkeys and apes	All ordinary laboratory animals. Monkeys and apes	Mice, squirrels, gophers, birds, monkeys	Hogs, sheep, cattle, goats, fowl
Sulfonamide therapy	Effective	Effective	Effective	No effect	Not known
Antibiotic therapy Penicillin	Not effective	Not effective except in high dosage	Not effective	Partially effective	Not known
Aureomycin	Effective	Effective	Effective	Effective	Not known
Chloromycetin	Not known	Not known	Effective	Effective	Not known
Terramycin	Effective	Effective	Effective	Effective	Not known

and vaginorectal and vaginovesicle fistulas. The disease always runs a protracted course with very little tendency to spontaneous healing. Death may result from secondary infection.

History of ocular involvement

Ocular involvement, although by no means a constant feature of the disease, has occurred in an important number of cases. The literature on this aspect of the subject has been well summarized by Macnie,[30] and more recently by Espildora and Coutts[31] in an extensive monograph. It is of interest that ocular lesions involving almost all the tissues of the eye have been observed in connection with the disease. The following reports are of particular interest:

In 1927, Koppel[32] observed episcleritis in two patients with lymphogranuloma venereum; they also had acute joint systems. Von Haam and Hartwell[33] (1936) reported an acute conjunctivitis in mice, monkeys, ferrets, cats, sheep, and calves that had been inoculated intracerebrally with the virus. The conjunctivitis was described as being hemorrhagic or purulent.

Weidman and Hunter[34] (1936) reported a case of lymphogranuloma venereum in a Negro, aged 35 years, who had had a pronounced puffiness of the lids which was considered to be an associated cutaneous change caused by the virus.

Levaditi, Schoen, and Reinie[35] (1932) produced the syndrome of Parinaud's oculoglandular conjunctivitis experimentally by inoculating the chimpanzee with the virus.

Levaditi, Bullock, Bash, and Desvignes[36] (1936) reported a patient with a unilateral follicular conjunctivitis of six months' duration with preauricular adenopathy but without corneal involvement; smears and cultures were negative for ordinary bacteria, the Frei test was positive, and an emulsion of material from the enlarged gland injected intracerebrally into a monkey resulted in typical lymphogranuloma venereum which was transferable to mice.

Satani and Sano[37] (1936) produced keratitis, conjunctivitis, and uveitis by inoculating the virus into the anterior chamber of rabbits and guinea pigs.

Ichijo[38] (1937) reported Parinaud's oculoglandular syndrome in two patients with positive Frei tests, and exudate from these eyes gave positive cutaneous tests in known Frei-positive patients. Hashimoto, Takenouchi, and Ichijo[39] (1937) reported an additional case of the syndrome in which ocular exudate served as a Frei antigen.

Applemans[40] (1939) reported an accidental conjunctival infection in a young woman physician who was working with the virus; the conjunctivitis was unilateral and oculoglandular in type. In Java, Ouwejan[41] (1939) found three patients with oculoglandular conjunctivitis in whom the Frei test was positive but from whom he was unable to isolate the virus or prove its presence in the lesions.

Curth, Curth, and Sanders[42] (1940) reported a case of conjunctivitis which was of unusual interest because of its long history, the thorough study to which it was subjected, and its response to sulfonamide therapy.

In May, 1932, after perverted intercourse with a West Indian Negress, the patient, a white man, developed a unilateral conjunctivitis with swelling of the preauricular and submaxillary nodes. The cornea soon became opaque and, after 1933, only light perception remained.

Antisyphilitic treatment, foreign proteins, and roentgen and radium irradiation all failed to affect the course of the disease. The case was presented several times by different ophthalmologists at the Academy of Medicine in New York as a Parinaud's conjunctivis of unknown etiology.

When the patient was first examined at Vanderbilt Clinic in 1938, a Frei test was found to be strongly positive and a biopsy showed a granulomatous type of inflammation. The virus was isolated from the conjunctiva. Frei antigen given intravenously

on four occasions failed to improve the condition but a course of sulfonamide, administered irregularly over a period of four months, led to cessation of all activity.

This case was of special interest because of the extragenital character of the primary lesion and the development of an elephantiasis of the lids resembling the elephantiasis of the labia known as esthiomene (fig. 3).

Fig. 3 (Thygeson). Primary keratoconjunctivitis due to lymphogranuloma venereum virus (M. lymphogranulomatis) with elephantiasis of the lids. (Case reported by Curth, Curth, and Sanders.)

Oliphant, Powell, and Perrin[43] (1942) reported an infection of the conjunctiva of a laboratory worker, 40 years of age, who had been experimenting with the virus. He developed a unilateral conjunctivitis of moderate severity which progressed to incipient keratitis with keratic precipitates. The virus of lymphogranuloma venereum was isolated from conjunctival washings and 10 days' treatment with sulfadiazine led to clinical cure. Neither preauricular adenopathy nor edema of the lids was mentioned in the report.

A number of fundus lesions have been reported in association with genitourinary lymphogranuloma venereum. Kitagawa[44] (1934) and Espildora and Coutts[45] (1934) reported peripapillary edema and tortuosity of the retinal vessels, and Kornblueth[46] (1936) reported a case with retinal hemorrhage.

Meyer and Reber[47] (1941) noted corneal ulceration in a case with systemic disease. Scheie, Crandall, and Henle[48] (1946) reported a type of sclerokeratitis, which localized characteristically at the upper limbus, in five patients with systemic lymphogranuloma venereum; in one patient they found inclusion bodies in a biopsy (fig. 4) taken from the corneal lesion.

In view of the marked cutaneous allergy induced by the virus in infected subjects, as indicated by the Frei test, the report of Sonck[49] is of particular interest. This Finnish observer collected 23 cases of lymphogranuloma venereum with allergic eye complications, including seven cases of phlyctenulosis, four of recurrent iritis, and two of episcleritis. The majority of these patients suffered from chronic proctitis or rectal stricture. In addition to the ocular symptoms, such other allergic manifestations as erythema nodosum and hydroarthrosus were common. All had negative Wassermann reactions and positive Frei tests.

With reference to the ocular lesions described by these numerous observers, it should be borne in mind that the virus was isolated from the conjunctivitis cases only; in all the others the etiologic diagnosis was presumptive.

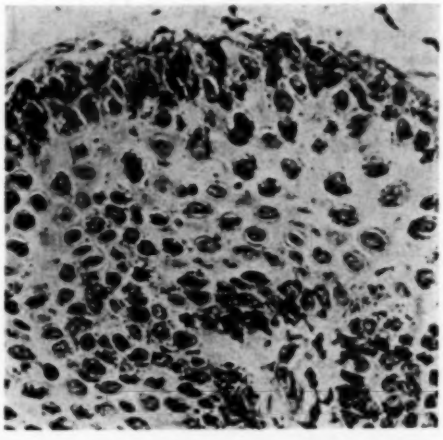

Fig. 4 (Thygeson). Inclusion bodies in biopsy from keratitis due to lymphogranuloma venereum. (Photomicrograph courtesy of Dr. H. G. Scheie.)

By way of summary it may be stated that two clinical eye manifestations of lymphogranuloma venereum appear to have been recognized; that is, an oculoglandular conjunctivitis, sometimes with elephantiasis of the lids (Curth, Curth, and Sanders[42]), and a sclerokeratitis with special characteristics (Scheie and co-workers[48]).

In view of the ease with which experimental uveitis may be produced in laboratory animals with the virus of lymphogranuloma venereum, and in view of the cases of uevitis cited by Espildora and Coutts[31] which responded to sulfonamide therapy, it would seem likely that cases of human uveitis will eventually be shown to have been caused by this virus (Macnie[30]).

In California, however, lymphogranuloma venereum cannot be a frequent cause of uveitis since only 13 Frei-positive individuals have been found among 367 cases of uveitis studied at the uveitis clinic of the University of California School of Medicine. It must be emphasized, moreover, that ocular lesions occurring in patients with systemic lymphogranuloma venereum must be considered merely coincidental unless the virus can be isolated from the ocular lesions themselves.

Properties of M. lymphogranulomatis

The virus of lymphogranuloma venereum is seen in affected cells (usually monocytes), in the characteristic inclusion bodies, and free in the exudate in the form of elementary bodies and, more rarely, initial bodies (fig. 5). Relatively pure suspensions of the virus bodies have been obtained by Rake and co-workers[29] from yolk-sac infections, and specific agglutination with immune serum has been demonstrated. The virus particles have also served as specific antigens in complement fixation and skin tests.

There seems to be some difference of opinion as to the particle size of this virus. In Giemsa-stained smears Miyagawa and associates[9] found the elementary body diameter to be 300mμ, while Thygeson,[50] in a study of mouse-brain material provided by Sanders, found it to be 250mμ, or exactly that of the virus particles of trachoma and inclusion conjunctivitis.

In filtration studies with Elford's gradocol membranes, Broom and Findlay[51] estimated the particle size to be from 120 to 180mμ, while in electron microscope studies of virus which had been propagated in the yolk sac

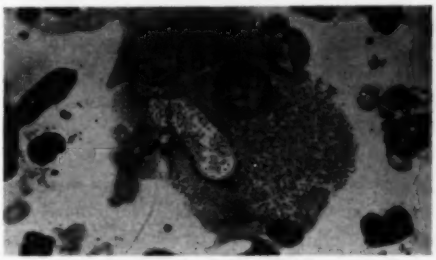

Fig. 5 (Thygeson). Lymphogranuloma venereum virus (M. lymphogranulomatis) in mouse-brain impression smear. (Giemsa stain. Drawn from a magnification of ×1,750.)

of developing chick embryos, a mean diameter of 438±470mμ was recorded by Kurotchin and co-workers.[52] It can be assumed that this latter estimation, which could hardly apply to the elementary bodies, refers to the intial bodies and intermediate forms.

The inclusion bodies of lymphogranuloma venereum constitute intracytoplasmic colonies of the virus and contain a minimum amount of matrix material which is most conspicuous in the early, "plaque" stage of the inclusion.

The virus appears to be only moderately resistant to heat and drying. At 37°C. it dries out in from two to four days, and at 56°C. it is inactivated within 10 minutes. In the frozen state it can be kept active for a year or more. In 50-percent glycerol, however, it remains active for from 7 to 14 days only, differing in this respect from vaccinia virus.

M. lymphogranulomatis does not appear to be capable of stimulating a potent immunity in spite of its predilection for cells of the

reticuloendothelial system which is so intimately connected with immunity. The poor immune response of the natural human disease is indicated by the rarity of spontaneous cures.

Antibodies which possess virucidal, agglutinative, and complement-fixing properties are found constantly in sera from infected patients but their titer is usually low. Experimental animals, particularly the guinea pig, can be hyperimmunized, however.

It is of interest that a serum prepared against lymphogranuloma venereum virus, while not protective against other members of the group, contains complement-fixing bodies which are frequently group-reacting. From this it may be deduced that there is a close antigenic similarity between members of the genus Miyagawanella and the genus Chlamydozoon (Rake, Shaffer, and Thygeson[53]).

Rake and Jones[54] made an important contribution when they found a toxin in association with the virus. It was easily demonstrated in heavily infected yolk sacs and was endotoxic in type. It was capable of killing mice on intravenous injection, and occasionally on intraperitoneal injection, and was readily inactivated by chemicals or by standing at room temperature. It gave specific complement fixation with sera from patients with lymphogranuloma venereum. Rake and Jones also found a heat-stable toxin and an ether-soluble antigen common to all the viruses of the genus Miyagawanella. The antigen appeared to be a protein-polysaccharide-lipoid complex.

M. lymphogranulomatis can be grown in tissue culture but isolation from the human disease is best accomplished by the intracerebral inoculation of mice or the injection into the yolk sac of the developing chick embryo with biopsy material. Inoculum grossly contaminated with bacteria can be treated with penicillin-streptomycin mixtures before being introduced into the yolk sac.

The virus is not highly infectious and the epidemiology of the disease parallels that of syphilis. Venereal transmission is the rule but, as in syphilis, occasional extragenital transfers have been recorded, including accidental infections among medical personnel in contact with cases and among laboratory technicians working with the virus.

Therapy

Prior to the introduction of the sulfonamides, lymphogranuloma venereum was treated with antimony compounds, such as fuadin, and with intravenous Frei antigen. The results were only partially successful, however.

The virus proved to be definitely susceptible to the sulfonamides but protracted treatment times were found to be necessary, particularly in the anorectal disease. Clinical cure was sometimes obtained in spite of persistence of the virus in the body.

The mechanism of action of the sulfonamides is not entirely understood but is virustatic rather than virucidal. Penicillin and streptomycin have little or no effect on the virus but aureomycin, chloromycetin, and terramycin are all active against it. The antibiotics are now the treatment of choice, but combined sulfonamide-antibiotic therapy is indicated in advanced and resistant cases.

Inclusion conjunctivitis virus (C. oculogenitale)

A benign form of ophthalmia neonatorum, unassociated with any pathogenic bacteria, was described by Morax[35] in 1903. In 1909, Stargardt[2] and Schmeichler[3] found, in conjunctival scrapings from conjunctivitis of the newborn, inclusions morphologically identical to those found by Halberstaedter and Prowazek[1] in trachoma.

In 1911, Lindner[36] defined the clinical characteristics of the disease and named it "Einschlussblennorrhoe" or "inclusion blennorrhea." The name "inclusion conjunctivitis" is to be preferred, however, in view of the nonpurulent character of the disease in adults.

In 1910, Wolfrum[57] reported experimental transmission of the disease to two adult eyes with conjunctival exudate from infants.

Searching for the origin of the disease, Halberstaedter and Prowazek[58] found typical inclusions in the genito-urinary tracts of mothers of affected babies and postulated the existence of an inclusion disease of the male and female genito-urinary tracts. This was supported by the studies of Lindner[59] and Heymann,[60] each of whom found inclusions in several cases of urethritis in the male, and later Fritsch, Hofstatter, and Lindner[61] produced a conjunctival infection in the baboon with urethral exudate from nongonococcal urethritis containing epithelial-cell inclusions.

Thygeson,[62] and Thygeson and Stone,[63] showed that inclusion conjunctivitis would respond rapidly to systemic administration of the sulfonamides and that the disease in the newborn would also respond to topical sulfonamide therapy. Braley and Sanders[64] reported its susceptibility to aureomycin. The failure of silver nitrate and penicillin prophylaxis to prevent the disease in the newborn has been noted by Allen and Barrere[65] and by Thygeson and co-workers.[66]

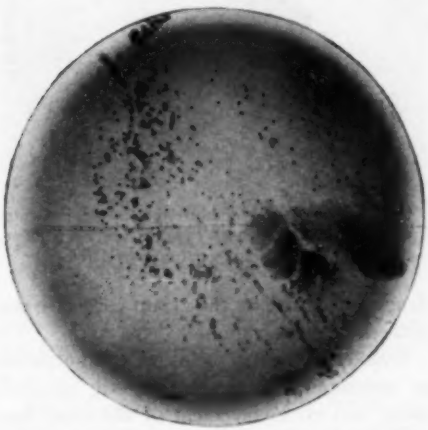

Fig. 6 (Thygeson). Elementary bodies of inclusion conjunctivitis. (Giemsa stain. ×2,000.)

PROPERTIES OF C. OCULOGENITALE

Inclusion conjunctivitis virus, or Chlamydozoon oculogenitale, like other members of the Chlamydozoaceae, is seen characteristically in elementary body form as a minute coccoid body about 250mμ in diameter (fig. 6) when stained with Giemsa stain. It is Gram-negative and stains poorly with ordinary aniline dyes, but with Giemsa or other blood strains it has the same reddish-blue coloration as the elementary body of trachoma.

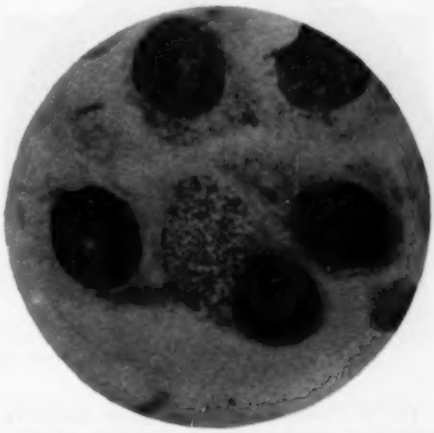

Fig. 7 (Thygeson). Elementary-body inclusion of inclusion blennorrhea with several retained initial bodies at the periphery. (Giemsa stain. ×2,000.)

The developmental cycle appears to be identical with that of C. trachomatis and has been studied by Thygeson[8] during the incubation period in inclusion conjunctivitis produced by experimental inoculation.

The study of scrapings taken at intervals after inoculation revealed that about 48 hours elapsed from the time the elementary body entered the epithelial cell until the cell ruptured, and that there were usually about three complete cycles during the five- or six-day incubation period. In the 48-hour period, the initial body phase of the cycle occupied only the first 15 or 20 hours, fully developed

elementary bodies predominating subsequently.

It is interesting that an occasional initial body appeared to undergo an arrest in development: isolated initial bodies (fig. 7) were sometimes to be found in inclusions otherwise containing only fully developed elementary bodies. Arrested development probably also explains the occasional presence of free initial bodies in secretion from acute cases; they must have been released from mature elementary body inclusions which have ruptured spontaneously. Phagocytosed elementary bodies are occasionally seen in neutrophilic leukocytes (fig. 8).

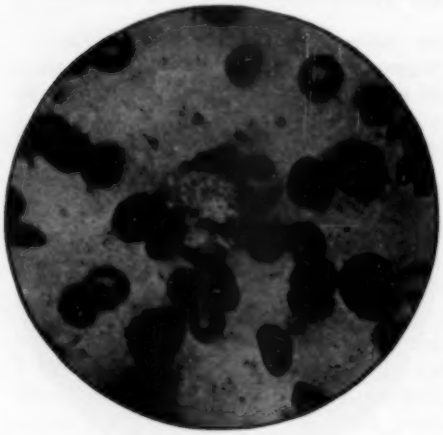

Fig. 8 (Thygeson). Phagocytized elementary bodies in a polymorphonuclear leukocyte. (Giemsa stain, ×1,750.)

The mature inclusion body shows the same carbohydrate matrix (fig. 9) which Rice[67] demonstrated for the trachoma inclusion, but Thygeson[68] found the matrix of the inclusion conjunctivitis inclusion to be inconstantly present and less dense. As in trachoma, the matrix gives the typical microchemical reactions for glycogen.

Inclusion conjunctivitis virus, unlike the typical viruses, has the ability to induce an exudate rich in polymorphonuclear leukocytes. This is particularly true of the acute disease in the newborn infant in which polymorphonuclear cells may constitute 90 percent or more of the leukocytes. As the acute stage passes, however, monocular cells become more prominent although they never entirely replace the polymorphonuclear cells.

Filtrability. Unlike C. trachomatis, C. oculogenitale filters with relative ease. This is not due to any difference in the particle size of the virus but rather to the more concentrated virus suspensions which can be obtained. Thygeson[8] found the virus to pass gradocol membranes of A.P.D.* 530mμ but to be retained regularly by membranes of A.P.D. 250mμ and less.

Tissue affinities. The tissue affinities appear to be sharply restricted, the virus having been demonstrated only in the stratified squamous epithelium of the conjunctiva and of the genital tract of humans, apes, and monkeys. So far it has not been seen in corneal epithelium although studies of this tissue have necessarily been limited by the danger of damaging the infant cornea in the process of examination.

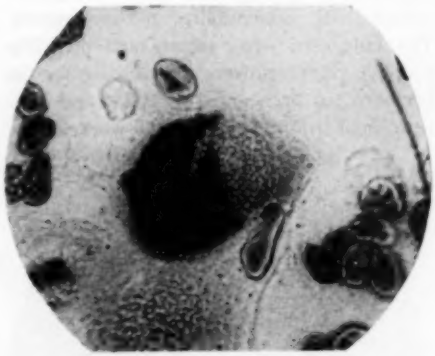

Fig. 9 (Thygeson). Inclusion body of inclusion conjunctivitis stained with Lugol's solution to demonstrate the carbohydrate matrix. (×1,750.)

Unlike trachoma, inclusion conjunctivitis is uncomplicated by lacrimal-sac involvement, and no involvement of the nasal mucous membrane has been reported in spite of

* Average pore diameter.

the fact that infectious material must of necessity pass into the nose through the nasolacrimal ducts.

Unlike C. trachomatis, C. oculogenitale has a greater affinity for the conjunctiva of the lower lid, and Braley[69] has suggested that the number of inclusions per 100 cells in scrapings from the upper and lower tarsal conjunctivas has differential value; in trachoma the numerator is always greater while in inclusion conjunctivitis the denominator is always greater.

In sections the inclusions are always most numerous in the superficial layers of the epithelium and are never to be found in the basal cells. Several inclusions in different stages of development are sometimes seen in a single cell (fig. 10).

Toxin production. A specific soluble toxin has not yet been certainly identified in this disease but it may be assumed that one exists by analogy with other members of the group. Indeed, the existence of such a toxin would seem to be the only reasonable explanation for the dense subepithelial infiltrate so characteristic of the disease in the newborn, and for the follicular hypertrophy so characteristic of the disease in the adult.

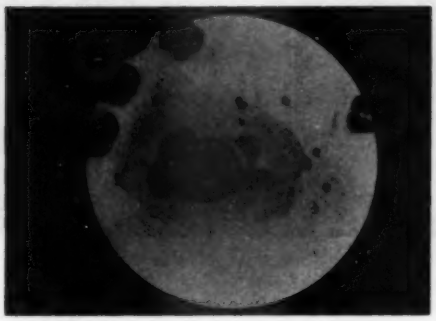

Fig. 10 (Thygeson). Multiple inclusions in a single cell. (Giemsa stain. ×1,000.)

Cultivability. Like trachoma virus, inclusion conjunctivitis virus has not yet been cultivated with certainty, either in tissue culture or on the chorioallantoic membrane or yolk sac of the developing egg, and like trachoma virus it dies out rapidly in tissue culture of explants.

In an extensive study Braley[70] was unable to grow the virus on either the chorioallantois of the developing chick embryo or in tissue culture, but after repeated "blind" mouse-brain passages in which material known to be infectious was used, he obtained a transmissible encephalitis-producing virus which also produced a follicular conjunctivitis in baboons. The agent grew readily on the chorioallantoic membrane and in the yolk sac of developing chick embryos and was lethal for the embryo itself.

Fig. 11 (Thygeson). Experimental unilateral inclusion conjunctivitis in the baboon showing characteristic ptosis.

Unlike C. oculogenitale, however, this virus had a particle size below the limits of visibility of the ordinary microscope and was not affected by sulfonamide therapy. Although it could not be identified by neutralization tests with any of the known mouse viruses, it was in all probability an adventitious agent demonstrated by mouse passage.

Experimental infections with C. oculogenitale

The virus is readily transmissible to the conjunctivas of man, monkey, and ape. All ordinary laboratory animals are resistant. It is of interest that the experimental disease in baboons (fig. 11) resembles the human disease. It is more severe than experimental trachoma and inclusion bodies are readily

demonstrable in conjunctival scrapings (fig. 12).

The 5-to-10-day delay in the appearance of clinical symptoms after parasitization of the epithelial cells, which corresponds to the long incubation period in most virus diseases, has never been explained satisfactorily. The time lag between the disappearance of the virus as a result of sulfonamide therapy, and the disappearance of the discharge and inflammatory signs, is usually shorter than the incubation period.

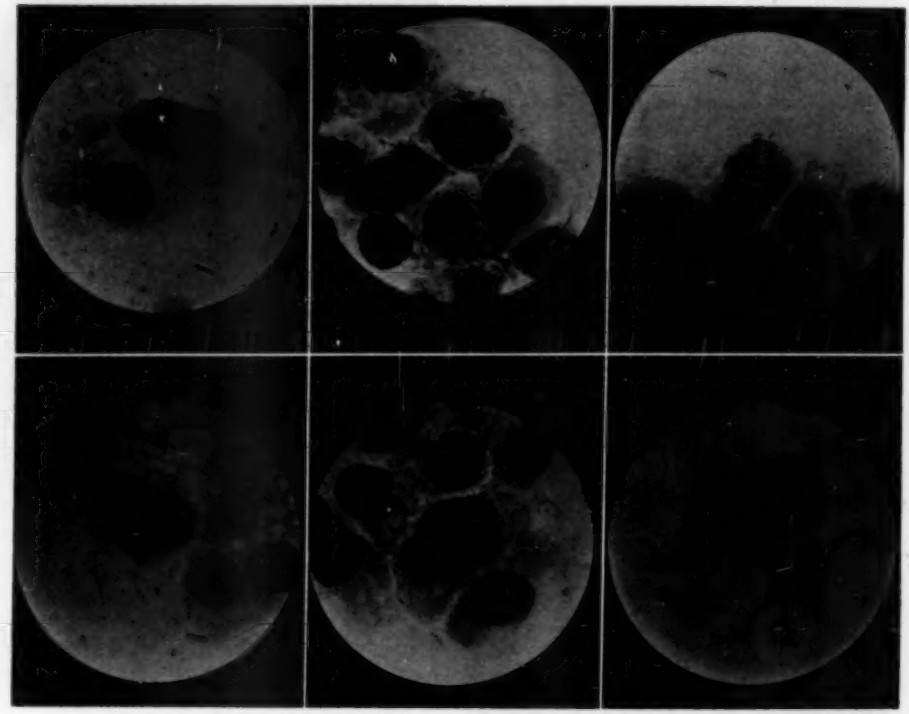

Fig. 12 (Thygeson). Inclusion bodies from experimental trachoma of the baboon. (×1,000.)

Genito-urinary infection with C. oculogenitale

Unlike trachoma virus, inclusion conjunctivitis virus has a normal extraocular habitat; that is, the genito-urinary tract of males and females. In spite of the fact that the genito-urinary localization was recognized as early as 1909, very little is known about this widespread but benign veneral disease.

Thygeson and Mengert[71] were able to show that the principal localization of the virus in the adult female was a narrow strip of transitional epithelium at the external os. The keratinized epithelium of the vagina and the glandular epithelium of the cervical canal appeared to be immune. These observers concluded that the cervical disease, although not strictly subclinical, was too mild to cause clinical symptoms. They were unable to demonstrate the virus in the female urethra and found no evidence to suggest that it caused disease of the uterus or adnexa.

Inclusion conjunctivitis virus is known to be one of the causes of nongonorrheal

urethritis in the male but the condition has never been recognized as a clinical entity by urologists. It is known to be benign in character and to run a clinical course to spontaneous healing in a matter of months. It is also known to occur frequently in association with gonorrheal urethritis (Thygeson and Stone[72]).

In view of the follicular hypertrophy so characteristic of the conjunctival infection, it would seem that the virus might also cause a follicular hypertrophy of the urethra, but although a urethritis follicularis[72] has been recognized it has not as yet been identified with inclusion virus infection.

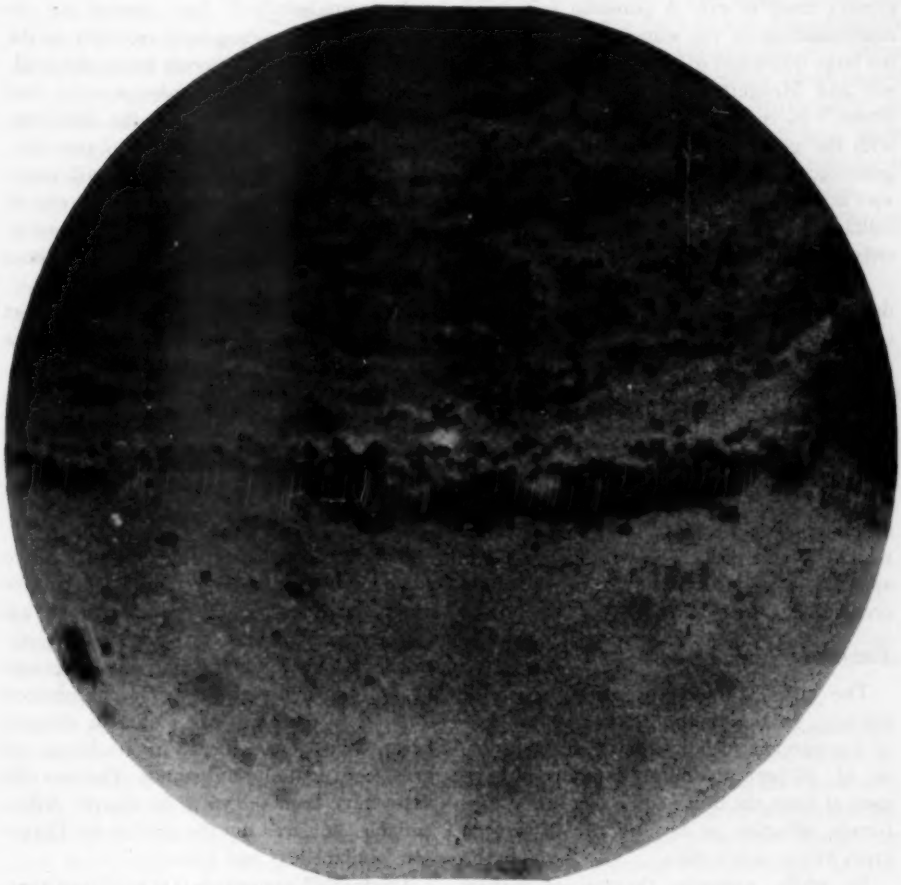

Fig. 13 (Thygeson). Elementary bodies in cervical scrapings from the mother of an infant with inclusion conjunctivitis. (Giesma stain. ×3,000.)

Epidemiology

C. oculogenitale parasitizes the epithelium of the genital tract primarily and ocular transmissions appear to be more or less accidental. In this respect the epidemiology parallels closely that of the gonococcus. The highest incidence of infection naturally is in the newborn infant, as a result of birth-canal contamination.

Swimming-pool transmission. The spread of the disease among swimmers in certain unchlorinated pools is believed to be due in most instances to transmission from genito-urinary tract to eye. A potential source of contamination of the water is suggested by the large quantities of virus found by Thygeson and Mengert,[71] and by Thygeson and Stone,[72] in cervical scrapings from women with the genito-urinary disease. Unlike the gonococcus, C. oculogenitale is able to survive in water, probably by virtue of its intracellular location in desquamated epithelial cells.

Accidental infections. A number of accidental infections of obstetricians and gynecologists have been reported by Thygeson and Mengert[71] and other observers. In one case a gynecologist was infected in one eye by a spurt of blood from a cervix during a routine dilation and curettage operation. In another case an obstetrician was spattered in the eyes during a delivery, and in a third case a gynecologist was spattered in the eyes while taking a routine cervical culture. It is apparent that the disease can be a definite occupational hazard.

Therapy

The virus is susceptible to sulfonamide therapy. In the infant, topical applications of five-percent sulfathiazole or sulfadiazine, or of 10-percent sulfacetimide ointment, used at least six times daily, have been uniformly effective in healing the disease in from five to seven days.

In adults systemic therapy is usually necessary, topical applications being less effective, probably due to the diluting effect of the tears which is not a problem in the newborn in whom tear function is minimal. No resistant cases have been encountered by me or have been reported in the literature.

The sulfonamides are not virucidal but apparently act by inhibiting the development of the virus intracellularly. This is indicated by the finding of inclusions regularly during the first two days of therapy, irregularly the third day, and never thereafter. The disappearance of the inclusions is apparently a result of the natural desquamation of the conjunctival epithelium.

Aureomycin[64, 74, 75] has proved to be equally effective when used topically in the newborn disease. No reports are as yet available on the effect of chloromycetin and terramycin but, in view of the similarity of their spectra to the spectrum of aureomycin, it seems likely that they also will prove to be effective. Penicillin is active only in very high concentrations and, as previously mentioned, is not protective when substituted for silver nitrate in the Crede prophylaxis.

No information is available as to the effect of sulfonamide or antibiotic therapy on the genito-urinary infection, but in all probability the same favorable results obtained in ocular cases would prevail.

The relation of C. oculogenitale to C. trachomatis

The relation of inclusion conjunctivitis to trachoma has excited considerable controversy, partly because of the unfortunate use of the term "genital trachoma" and "paratrachoma" by Lindner,[76] and partly because of the similarity of the early conjunctival findings in the adult cases of both diseases before the development, in trachoma, of gross cicatrization and pannus. The two diseases have been shown to be sharply differentiable, however, by the studies of Thygeson,[8] Julianelle,[77] and Allen.[78]

Lindner's[76] suggestion that trachoma virus is a modified inclusion conjunctivitis virus whose pathogenicity for the conjunctiva has been increased by passage from eye to eye, is interesting to speculate upon. Experimental proof of this hypothesis is of course difficult to obtain. Allen[78] transmitted the disease from eye to eye through 40 consecutive passages and was unable to show any modification.

It is noteworthy that there is no parallelism between the frequency of trachoma and

inclusion conjunctivitis. In Egypt, for example, where trachoma is almost universal, inclusion conjunctivitis is virtually unknown; I have been unable to find any reference to its occurrence in Egypt and found no case of it there during a three months' study of trachoma in the winter of 1931-32.

In my experience, inclusion conjunctivitis has been common and severe among American Negroes, while trachoma has been extremely rare. This would seem to be an unlikely finding if the two diseases were closely related.

In discussing this hypothesis, however, it should be recalled that Braley[69] was able to produce with epithelial scrapings from trachoma an inflammation of the cervix of the baboon which was similar to that produced with inclusion conjunctivitis virus. This was later confirmed by Okamura, Takano, and Mitsui[79] in human volunteers.

Trachoma virus
(C. trachomatis)

Trachoma is by far the most important of the diseases caused by any of the Chlamydozoaceae, with respect not only to the degree of ocular damage but also to the economic loss involved. It has been estimated that 20 percent of the world's population is affected by the disease and in some countries the incidence is extraordinarily high; for example, 90 percent in Egypt.

Trachoma is the only eye disease of sufficient worldwide importance to justify the publication of a special journal devoted to it —the *Revue Internationale du Trachome*, founded in 1923 by Victor Morax and Charles Nicolle.

In the United States sporadic cases are still seen in all parts of the country but the disease remains a major public health problem only among the Indians of the southwest and in the white population of the so-called "trachoma belt" of states—West Virginia, Indiana, Kentucky, Tennessee, Illinois, Missouri, Arkansas, and Oklahoma.

Properties of C. trachomatis

In Giemsa-stained preparations the elementary body of trachoma (fig. 1) measures 250mμ in diameter. The initial bodies and transition forms vary in size from approximately 300mμ up to a maximum of 1,500mμ in greatest diameter. Accurate measurement by differential filtration, centrifugation, or electron microscope has not yet been made but the diameter of the smallest particles is probably in the neighborhood of 200mμ.

There are no morphologic or staining

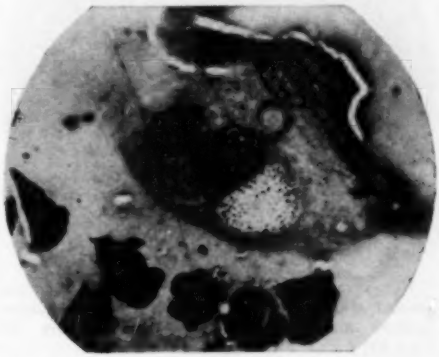

Fig. 14 (Thygeson). Inclusion body of trachoma showing elementary and initial body forms of the virus. (Giemsa stain. ×1,500.)

differences between the virus bodies of trachoma and the virus bodies of inclusion conjunctivitis. With Giemsa stain the elementary bodies take a reddish-blue coloration and the initial bodies always a pure blue; that is, the differential staining characteristic of the Chlamydozoaceae as a whole.

The inclusion bodies of trachoma are also identical morphologically with those of inclusion conjunctivitis, showing the same elementary body-initial body variation (fig. 14) of the component virus particles and the same carbohydrate matrix (fig. 15) which takes a glycogen stain with iodine. As previously mentioned, however, this matrix is more abundant in the trachoma inclusion than in the inclusion conjunctivitis inclusion.

As in inclusion conjunctivitis, the inclu-

sion bodies of trachoma are most numerous in the early and acute phase of the disease but can be found, with some difficulty, in chronic cases and in exacerbations of old disease.

Like C. oculogenitale, C. trachomatis stimulates a polymorphonuclear exudate,[80] abundant in acute cases and scanty in chronic cases, the amount paralleling closely the concentration of virus as measured by the number of inclusions present.

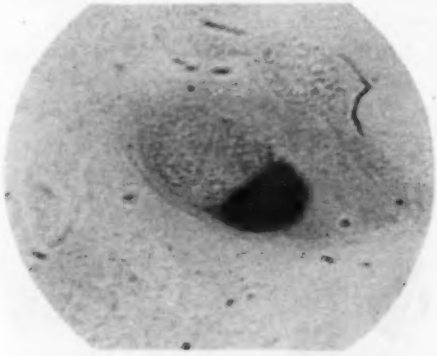

Fig. 15 (Thygeson). Inclusion body of trachoma stained with iodine solution to show the carbohydrate matrix. Same cells as in Figure 14. (×1,500.)

Filtrability. Trachoma virus was first filtered by Nicolle, Cuenod, and Blaizot,[81] in 1912. These observers used a Berkefeld-V filter so modified by the reduction of its filtration surface as to prevent excessive loss of virus. This they accomplished by cementing a button of Berkefeld-V substance into a glass tube. Ordinary filtration techniques have been found to be unsuitable for trachoma studies because of the high loss of virus by adsorption.

In 1935, Thygeson, Proctor, and Richards[82] confirmed these positive filtration findings, in both human and baboon experiments, with gradocol membranes of 0.6mμ A.P.D.

In their final experiment the human volunteer developed a typical trachoma which required a year of treatment to cure and was accompanied by cicatrization and pannus formation. The filtrability of trachoma virus was again confirmed by Julianelle and co-workers[83] who employed Berkefeld-V filters and Macacus rhesus monkeys.

Tissue affinities. C. trachomatis, like C. oculogenitale, is strictly epitheliotropic. Although elementary and initial bodies are occasionally found in neutrophilic leukocytes, there is no evidence of their multiplication within these cells.

The virus has never been seen in subepithelial tissues and all attempts to infect subepithelial tissues with it, in both animal and human experiments (Michâil and Vancea,[84] Thygeson and Richards,[85] and Okamura and Mitsui[86]), have failed. The experiments of Okamura and Mitsui are illustrative.

These Japanese observers passed trachoma virus through the skin of the upper lid into the upper fornix of each of a number of human volunteers and failed to obtain infection. In each case the conjunctiva was shown later to be susceptible to direct inoculation with the virus.

Unlike the inclusions of inclusion conjunctivitis, which are always most numerous in the lower palpebral conjunctiva and in the conjunctiva of the fornix, the inclusions of trachoma are most numerous in the conjunctiva of the upper lid. Their location in sections would seem to indicate that the virus prefers the superficial cells of the conjunctiva, does not involve the basal cells, and tends to spare cells containing pigment granules. As we shall see later, the relative resistance of young epithelial cells has an important bearing on therapy.

The high incidence of dacryocystitis in trachoma would indicate that the epithelium of the lacrimal sac is parasitized on occasion. In histologic studies of the lacrimal sac, Mitsui[87] demonstrated typical trachoma follicles in the subepithelial tissues and abundant inclusions in the epithelium. On the other hand, although the virus is known to pass into the nose through the nasolacrimal duct, inclusions have never been demon-

strated in nasal epithelium and no associated rhinitis has ever been recognized.

Unlike C. oculogenitale, C. trachomatis does not normally involve genital epithelium, but Braley[69] produced an experimental infection with it in the cervical epithelium of the baboon, and Okamura and Mitsui[85] were equally successful in their attempts to infect the cervical epithelium of human volunteers.

Toxin production. Since trachoma virus has never been found in subepithelial tissues in spite of the fact that the principal pathology of the disease is subepithelial, a soluble toxin must be presumed to exist if the necrotizing action so characteristic of the virus is to be explained.

Soluble toxins have been demonstrated for the agents of psittacosis and lymphogranuloma venereum and will, in all probability, eventually be demonstrated for trachoma in spite of technical difficulties. For the present there is a certain amount of cytologic evidence in favor of the existence of such a toxin; this includes: (1) The characteristic polymorphonuclear reaction, particularly in acute cases; (2) the necrotic changes in follicular cells; and (3) the presence of numerous macrophages (Leber cells) which act as scavenger cells.

Cultivability. Trachoma virus has not yet been cultivated with certainty. Several claims of successful cultivation on the chorioallantoic membrane of the developing egg have been made but they have been based on the morphologic demonstration of the virus in tissue rather than on transmission experiments.

In an extensive cultivation study at the trachoma school at Fort Apache, Arizona, Thygeson[89] was able to cultivate conjunctival epithelium in Carrel flasks but was unable to infect the growing tissues with filtered or unfiltered trachomatous material. He was also able to cultivate trachomatous conjunctival epithelium (fig. 16) from active cases of the disease but the virus failed to proliferate in the newly formed epithelium and on the contrary tended to die out rapidly, the cultures becoming noninfectious for baboons within a few days.

Julianelle[90] and Bland[91] were totally unsuccessful in their efforts to obtain cultivation. Ishihara and co-workers,[92] on the other hand, claimed the demonstration of inclusions in tissue culture but could not maintain the virus in serial culture. The numerous reports of Poleff,[93] claiming cultivation in tissue culture, are based on morphologic evidence only and must therefore be considered inconclusive.

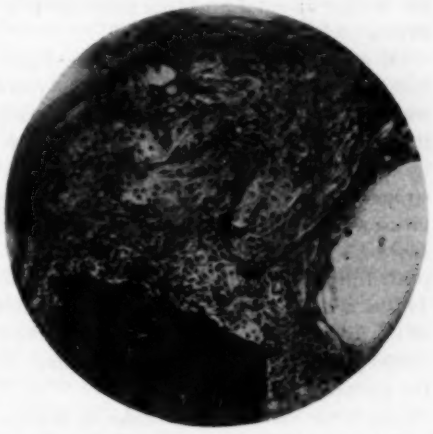

Fig. 16 (Thygeson). Fifty-six-hour epithelial growth from a patient with Stage I trachoma (with inclusions). (Giemsa stain. ×250.)

Experimental infections with C. trachomatis

Trachoma virus is capable of infecting humans and various species of monkeys and apes. The experimental human disease almost always has an acute onset but in other respects its clinical course is like that of the natural disease. In monkeys and apes the experimental disease is never acute but always of low intensity, and has a prolonged incubation period unlike the five- to seven-day incubation period of the human disease. The experimental animal disease appears as a chronic follicular conjunctivitis without

any of the complications of the human disease, such as cicatrization or pannus. It heals spontaneously and in this respect is also unlike the human disease.

It is interesting that experimental inclusion conjunctivitis is a more severe disease, and much more like its human counterpart, than experimental trachoma. In experimental inclusion conjunctivitis, inclusions can be demonstrated without great difficulty, but in experimental trachoma there are usually no inclusions to be found.

Of special interest is the experiment performed by Bland[94] in which trachoma virus was trasmitted to Grivet monkeys, carried through four monkey passages, and then retransferred to man. Inclusions were demonstrated in the original case from which the virus was obtained, could not be found in any of the four passages, and then reappeared in the experimental human infection. This could best be explained on the basis of the very low intensity of the experimental monkey disease rather than on any change in the morphology of the virus.

The occurrence of a spontaneous folliculosis in monkeys was noted by Wilson,[95] and more recently by Bland,[94] as a major obstacle to successful trachoma research. Although experimental trachoma can usually be distinguished clinically from the spontaneous disease with reasonable certainty, the differentiation is not sufficiently clear-cut to remove all possibility of error.

Immunology

Infection with trachoma virus fails to produce immunity to the disease. Healed trachoma cases have been repeatedly reinfected and there has been no difficulty in reinfecting monkeys after spontaneous cure of experimental trachoma. The new disease differs in no way from the original infection.

The experiments of Rake, Shaffer, and Thygeson,[58] however, indicate that group complement-fixing antibodies do develop in trachoma, as well as in inclusion conjunctivitis, although their concentration is apparently insufficient to influence the course of the disease.

It is noteworthy that Negroes show a relative resistance to trachoma. The disease has never been a problem among them and, when it occurs, seems to pursue a milder course than in the white population. This is particularly interesting in view of the fact that the Negro seems to have no resistance to the virus of inclusion conjunctivitis.

Among the dark Mediterranean peoples, for example, the Egyptians, trachoma has a high incidence but tends to be mild. In Egypt gonorrheal ophthalmia rather than trachoma is the main cause of blindness. In the Egyptians themselves, trachoma is almost never acute and the conjunctivitis may persist for years without visual damage. On the other hand, as pointed out by Wilson,[96] trachoma contracted by northern Europeans in Egypt may be extraordinarily severe, with pannus and corneal ulceration leading rapidly to loss of vision.

The reason for this relative immunity among dark-skinned people is not understood but there is certainly a parallelism between racial resistance and skin pigmentation. In an unpublished study, Thygeson has suggested that epithelial cells containing pigment granules are less likely to be infected than cells without pigment; he found that inclusions tended to spare cells containing pigment granules.

Epidemiology

Trachoma virus spreads from eye to eye. Attempts to incriminate arthropods have been unsuccessful. The fly has been suggested as an agent of transmission in Egypt, but it must be only an occasional carrier in view of the infrequency of trachoma in the European population of Egypt which is also exposed to fly contamination.

It has been recognized throughout the world that the mother acts as the principal transmitter of the disease to her children by virtue of her necessarily intimate contact with them. This was shown by Thygeson and

Forster[97] in a study among the Apache Indians in whom the incidence of trachoma among preschool children was found to be as high as the incidence among adults. They also found that in families in which the father only was infected, the children were apt to escape.

A number of instances of accidental infection of doctors have been recorded. In these cases infection usually occurred during operative procedures, such as grattage or follicular expression, in which material from the conjunctiva was transferred directly to the eye of the physician.

In the United States, however, sporadic cases of trachoma have occurred in which it has been difficult or impossible to determine the source of infection in spite of careful search for contacts. This suggests the possibility that there is a still unknown method of transmission.

On the basis of the finding of inclusion bodies in epithelial scrapings from clinically normal conjunctivas, Bodian[98] has suggested that a carrier state exists in trachoma. Since his findings were entirely morphologic and uncontrolled by animal or human transmission experiments, the question can by no means be considered settled.

In view of the confusion which has obtained with reference to the recognition of the Halberstaedter-Prowazek type of inclusion body, conclusions based on morphologic studies must be subjected to the most critical analysis. It has been established, however, that inclusions are demonstrable during the incubation periods of both experimental trachoma and experimental inclusion conjunctivitis before the onset of visible changes.

Epidemiologic relation of C. trachomatis to conjunctival bacteria. No symbiotic or other relationship to any of the bacteria of epidemic conjunctivitis has been demonstrated for trachoma virus, in spite of the fact that in Egypt and the Middle East pure trachoma is a rarity.

It is true that the so-called "Ophthalmia Aegyptiaca" which devastated the armies of Napoleon is a combination of trachoma with Koch-Weeks conjunctivitis or gonorrheal ophthalmia, or both (Wilson[99]), but the association is not obligatory.

In many parts of the world, trachoma, at least in its precicatricial stages, is a pure disease and the virus passes from eye to eye without the aid of a bacterial carrier. There is no doubt, however, that the abundant exudate produced by secondary bacterial infection increases the infectivity of trachoma. Many cases are on record in which one member of a family only was infected, transmission to others occurring only when an acute bacterial conjunctivitis was superimposed on the chronic trachoma.

Therapy

It has been known since antiquity that copper sulfate or other cauterizing substance applied frequently to the trachomatous conjunctiva was of therapeutic value. The mechanism of this healing process has never been adequately explained.

Thygeson has advanced the theory that any substance which increases the desquamation of the conjunctival epithelium and stimulates the basal cells to proliferate will be curative in the sense that newly formed epithelial cells are resistant to infection; as a result, the virus eventually finds no susceptible cells to infect, and normal desquamation finally eliminates the last virus-containing cells.

The dissolving effects of bile salts on trachoma inclusions was described early by Lindner[76] and it is interesting that in the Bible there is a reference to the treatment of "ophthalmia" by the use of fish bile.

The ordinary conjunctival antiseptics are useful in controlling the secondary infections so common in trachoma but have no effect on the trachoma itself. They destroy the virus on direct contact in in vitro experiments but their in vivo effect is undoubtedly prevented by the intracellular location of the virus.

Tarsectomy, which was once a very popular treatment of trachoma, probably acted by removing the most susceptible tissues from the action of the virus.

The demonstration of the antitrachomatous activity of the sulfonamides in 1938 by Loe[100] and others was the first major advance in trachoma therapy since copper sulfate was introduced by the Egyptians in antiquity.

In Europe and the United States the sulfonamides have been found to be almost uniformly effective except in late cicatricial cases with complications, such as meibomitis, trichiasis, xerosis, and keratitis sicca.

The results obtained in Egypt, the Middle East, and China, however, have been generally poor. This relative lack of success has not been adequately explained but may be accounted for in part by the high rate of reinfection in these areas and in part by the insufficiently prolonged treatment times employed in some series of cases. As in the sulfonamide therapy of lymphogranuloma venereum, prolonged treatment times in trachoma have proved to be more important than the maintenance of high blood levels of the drug.

In the United States, Thygeson[101] has encountered no sulfonamide-resistant cases. Even in old, complicated, cicatrical cases, in which symptoms have continued after therapy, C. trachomatis has apparently disappeared permanently from conjunctival scrapings. In such cases residual inflammation could be accounted for readily on the basis of the persistence of complicating factors, some of which, for example, trichiasis, have ultimately required surgical treatment.

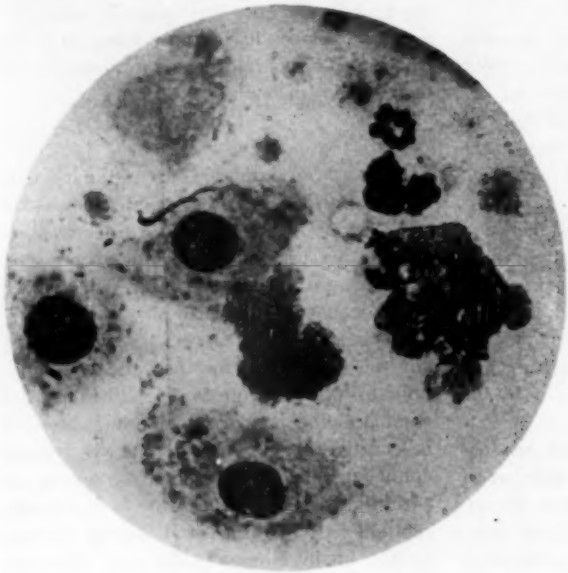

Fig. 17 (Thygeson). Colesiota conjunctivae from infectious ophthalmia of sheep. Mass of elementary-body forms extended from cell. (Giemsa stain. ×1,700. Courtesy of Dr. J. D. W. A. Coles.)

The action of the sulfonamides on C. trachomatis is still not understood but the experiments of Julianelle[102] indicated that there is no direct action on the virus in vitro. Richards, Forster, and Thygeson[103] showed that sulfonamide-treated cases became noninfectious for baboons after the first 48 hours, simultaneously with the disappearance of C. trachomatis from conjunctival scrapings. The sulfonamides would seem to act by interfering with the intracellular develop-

ment of the virus rather than by any direct virucidal action.

Penicillin and streptomycin have had no effect on trachoma except in cases complicated by secondary infection, but aureomycin seems to be significantly antitrachomatous. In a small series, Thygeson[104] found the effect of the oral administration of aureomycin to be comparable to that of the sulfonamides, and Moutinho, Monteiro Grillo, and Serrao de Moura, [105] and later Boase,[106] have found it to have dramatic effect when applied topically in solution or ointment form.

Mitsui[107] has employed both aureomycin and terramycin with success, but no reports are as yet available on the antitrachomatous activity of chloromycetin. The fact that these three antibiotics have similar spectra suggests, however, that all three will ultimately be found to be valuable in the treatment of the disease.

The Colesiota
(C. conjunctivae)

Infectious or specific ophthalmia of sheep is an epidemic disease which in South Africa in some years affects as many as 25 percent of the sheep. It starts as an acute purulent conjunctivitis with secondary keratitis and develops pannus and corneal ulceration. Johnson[108] found pannus in 80 percent of a flock of 200 infected animals, and superficial ulcers in five percent. In a few cases Coles[20] noted perforating ulcers with panophthalmitis and subsequent phthisis bulbi. The disease has been observed in Africa, New Zealand, Australia, and the United States and probably has a worldwide distribution.

Coles called the organism he found in conjunctival scrapings "Rickettsia conjunctivae" because of its rickettsialike morphology, but the absence of an arthropod vector has precluded it from classification with the Rickettsiaceae.

The presence of initial and elementary body forms, on the other hand, provides a logical basis for its inclusion among the Chlamydozoaceae in spite of important morphologic differences between it and the other members of this group. For the present, at least, it is being considered as the sole member of a third genus, the Colesiota, of this family and has been given the name Colesiota conjunctivae.

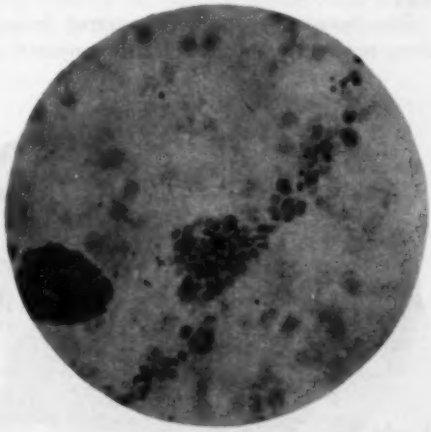

Fig. 18 (Thygeson). Colesiota conjunctivae from infectious ophthalmia of sheep. Extracellular initial body forms. (Giemsa stain. ×1,700. Courtesy of Dr. J. D. W. A. Coles.)

Properties of C. conjunctivae

Coles found the organisms consistently in diseased eyes but he also found them occasionally in normal eyes, possibly during the incubation period of the disease. They were seen characteristically in the cytoplasm of affected cells but occasionally extracellularly and in neutrophils.

The organism was pleomorphic and showed small, solidly staining "elementary body" forms (fig. 17) 500mμ in diameter, and large, coccobacillary "initial body" forms (fig. 18). Almost all the initial body forms, like those of other Chlamydozoaceae, stained bipolarly with Giemsa stain. Ring forms were common.

In the cytoplasm of the epithelial cells, clumping in inclusionlike masses was characteristic although many cells showed the diffuse distribution of the organisms (fig.

19) characteristic of most of the Rickettsiaceae. Extracellular masses of the organisms could also be seen. They were Gram-negative and stained with the ordinary bacteriologic dyes, although not as well as bacteria. No motility was observed in hanging-drop preparations of conjunctival scrapings.

The disease has been transmitted from sheep to sheep by inoculation with conjunctival exudate; the incubation period was about 48 hours (Johnson[108]). Conjunctival secretion was found to lose its infecting power in from 48 to 72 hours when kept at refrigerator temperature. The causal agent does not pass ordinary porcelain or diatomaceous earth filters and has not yet been cultivated.

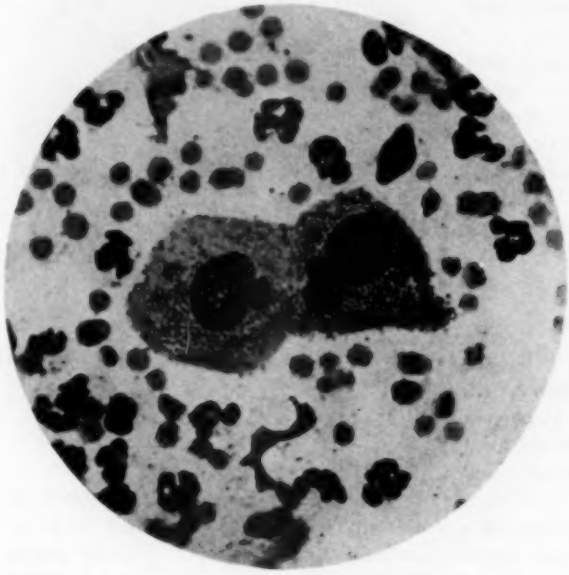

Fig. 19 (Thygeson). Colesiota conjunctivae from infectious ophthalmia of sheep, showing diffuse distribution of the organisms in the cells. (Giemsa stain. ×1,200. Courtesy of Dr. J. D. W. A. Coles.)

C. CONJUNCTIVAE IN KERATOCONJUNCTIVITIS OF CATTLE, GOATS, AND HOGS

In 1933, Coles[109] discovered intracellular bodies (figs. 20 and 21) in ophthalmia of cattle which were similar to those he had found in the infectious ophthalmia of sheep, and, in 1935, he found them in an extremely mild keratoconjunctivitis of goats[110] and in the conjunctivitis of hogs originally described by Uhlenhuth and Boeing[111] in 1910.

In the goat ophthalmia, the organisms were similar in all respects to C. conjunctivae, showing the same elementary body-initial body variation, elementary bodies of the same size (500mμ) which stained the same reddish color, and relatively large initial body forms which stained the same bluish color. Coles noted that up to 80 percent of the epithelial cells in representative slides were parasitized.

The morphologically identical organism he found in the ophthalmia of cattle he named "Rickettsia conjunctivae bovis." As in the disease in the sheep and goats, he was unable to find an arthropod vector. The parasites were always found in the early stages of the disease at a time when the leukocytic reaction was neutrophilic in type. They were transmissible from eye to eye by means of the exudate and had an incubation period of three days. Clinical disease did not develop,

however, and Coles noted that all attempts to transmit the clinical disease in South Africa had failed. He was unable to conclude, therefore, that the parasite was the cause of the disease.

In 1935, while in the United States, Coles[112] again found the intracellular bodies in the conjunctivitis of hogs which were first reported by Uhlenhuth and Boeing[111] in Germany in 1910. These German workers described the finding of inclusion bodies, similar to those occurring in trachoma, in the conjunctival scrapings of a high percentage of hogs suffering from hog cholera. This finding was apparently confirmed by Himmelberger[113] in 1916.

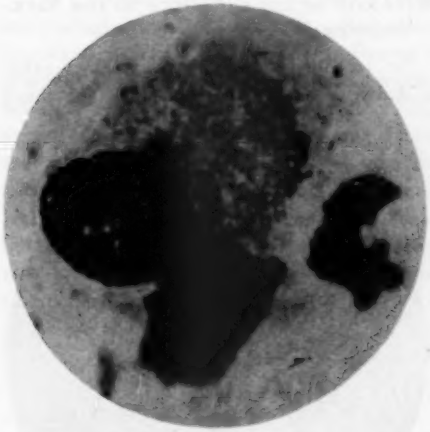

Fig. 20 (Thygeson). Colesiota conjunctivae in epithelial scrapings from conjunctivitis of cattle, showing conglomeration of the organisms into an inclusionlike mass. (Giemsa stain. ×1,400. Courtesy of Dr. J. D. W. A. Coles.)

Fig. 21 (Thygeson). Colesiota conjunctivae in epithelial scrapings from conjunctivitis of cattle, showing diffuse distribution of the organisms in the cytoplasm. (Giemsa stain. ×1,400. Courtesy of J. D. W. A. Coles.)

While conducting investigations on trachoma in Iowa in 1934, Thygeson[114] made a number of inoculations of hogs with hog-cholera virus but was unable to demonstrate intracellular bodies in conjunctival scrapings. In 1935, Morris[115] reinvestigated this problem and was also unable to find inclusions following the inoculation of hogs with the virus by various routes.

One hog, both before and after inoculation, displayed large masses in epithelial cells. They were composed of tiny, rodlike elements staining pale blue, deep blue, or occasionally deep pink with Giemsa stain. According to Morris, these bodies did not resemble the inclusions of trachoma.

Coles was of the opinion that the bodies described by the German workers had nothing to do with hog cholera but were related to hog ophthalmia which might have been a secondary infection in the cases studied. Coles described the bodies he found in the hog ophthalmia (figs. 22 and 23) as being morphologically identical with his previously described "Rickettsia conjunctivae."

In 1940, Coles[116] reported on a study of ocular roup in domestic fowls. Ocular roup is apparently a symptom-complex of multiple causes characterized by conjunctivitis with purulent discharge, cheesy exudate beneath the nictitating membrane, keratitis, and occasionally panophthalmitis. There is ordinarily an associated rhinitis, stomatitis, pharyngitis, laryngitis, and subcutaneous abscesses over the cranium. Occasionally cases are seen, however, in which only the

eyes are affected and in such cases Coles was able to find rickettsialike bodies.

By means of epithelial scrapings the disease was transmitted to normal birds in about 50 percent of attempts. The organisms appeared simultaneously with the clinical disease after an incubation period of approximately two days. The disease starts as a conjunctivitis with inflammation and swelling, particularly of the conjunctiva of the lower lid, and with a purulent exudate, followed by a keratitis with pannus formation.

The acute reaction usually subsides in about 15 days but may persist for as long as a month. Cicatrization of the nictitating membrane may be a complication. Severe systemic symptoms occasionally occur. Coles was unable to effect a cure with sulfonamide therapy.

In his description of the parasites, Coles noted their resemblance to his other organisms and proposed the name "Rickettsia conjunctivae galli" for them. He noted that the smallest elements were about 0.3mμ in diameter and the largest about 1.5mμ in length, and that the parasites tended to form colonies which were not attracted to the nuclei as they are in trachoma and inclusion conjunctivitis. He noted that the organisms were numerous at onset of the disease but disappeared with healing as the pus cells were replaced by monocytes and lymphocytes. Cultivation was not obtained.

Relation of the Colesiota to the Rickettsiaceae

It would seem that, unlike other Chlamydozoaceae, the Colesiota are much more closely related to the Rickettsiaceae than to the typical viruses. They are somewhat larger than other members of the Chlamydozoaceae, show less clear-cut inclusion-body formation, and are more pleomorphic.

Furthermore, while forming colonies resembling inclusions, no matrix has been reported for them and their lack of sulfonamide sensitivity sets them apart from the agents of trachoma, inclusion conjunctivitis, and lymphogranuloma venereum.

Fig. 22 (Thygeson). Colesiota conjunctivae in epithelial scrapings from conjunctivitis of a hog, showing inclusionlike conglomerations of organisms. (Giemsa stain. ×1,400. Courtesy of Dr. J. D. W. A. Coles.)

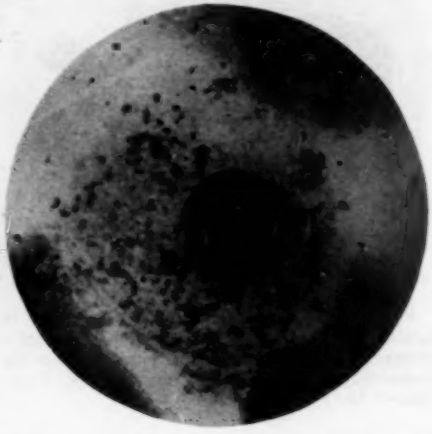

Fig. 23 (Thygeson). Colesiota conjunctivae in epithelial scrapings from conjunctivitis in a hog, showing rickettsialike diffuse cytoplasmic distribution of the organisms. (Giemsa stain. ×1,400. Courtesy of Dr. J. D. W. A. Coles.)

On the other hand, the Colesiota differs from the Rickettsiaceae in having no arthropod vector. Although Coles suggested that the common fly was instrumental in transmitting the ophthalmia of fowls, there seems to be nothing to suggest that the fly acts as an intermediate host. Unlike the Colesiota, most of the Rickettsiaceae have an affinity for the endothelial tissues of the body and are not epithelial parasites.

The Colesiota would seem to bear a close morphologic resemblance to Rickettsia ruminantium, now classified in Bergey's *Manual*[117] as Cowdria ruminantium, a member of a new genus which serves as a link in the chain of organisms extending from the typical large viruses to the smaller bacteria, by way of the Chlamydozoaceae and Rickettsiaceae. It would seem more than likely that additional studies will uncover new facts that will necessitate a reclassification of the Colesiota.

Summary

A newly defined group of viral agents, occupying an intermediate position between the typical large viruses and the Rickettsiaceae, carries the family name of Chlamydozoaceae and has three genera, Miyagawanella, Chlamydozoon, and Colesiota. The members of this group are related to the typical viruses by virtue of their filtrability and inclusion-body formation, and are related to the Rickettsiaceae by virtue of their size, their clearly microorganismal nature, their tinctorial properties, and their susceptibility to chemotherapy. While the Colesiota have been placed in this group tentatively by Rake, they more closely resemble the Rickettsiaceae and it is probable that future studies will necessitate their reclassification.

87 North Sixth Street.

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VISUAL ILLUSIONS IN NIGHT FLYING*

HENRY A. IMUS, LT. COMDR. (MSC) USNR (INACTIVE), ASHTON GRAYBIEL, CAPT. (MC) USN, ROBERT H. BROWN, PH.D., AND JORMA I. NIVEN, PH.D.
Pensacola, Florida

Research in visual illusions related to flying was initiated early in 1944 because of a series of unusual aircraft accidents which occurred at the Naval Air Training Bases at Pensacola. Investigations of these accidents revealed what seemed to be a common factor —confusion or disorientation of the pilot just prior to the crash.

In order to determine the kind and frequency of visual illusions in flight, a survey and controlled interview experiment was undertaken. Vinacke[1] interviewed 77 Naval aviators and concluded that various types of disorientation may occur in any type of aircraft at any altitude and may follow almost any type of maneuver. However, this vertigo, as he calls it, is most likely to occur under extremely hazardous conditions, such as under adverse weather and visibility conditions and at night.

Sensory illusions predominate (69 percent). The remaining proportion is attributable to psychologic and emotional factors or to the establishment of conflicting clues. His results called attention to the need for further experimentation on both sensory and psychologic factors, and for an educational approach to the problem for the purpose of eliminating some of the mystery and fear involved.

On the basis of a suggestion by Dr. Walter R. Miles that autokinesis might be a factor, experiments[2] were conducted to study this phenomenon. Both laboratory experiments and tests in flight were conducted under controlled conditions in order to determine the characteristics, incidence, temporal factors, and magnitude of the phenomenon.

These studies showed that the autokinetic illusion can be experienced by normal persons under conditions which favor its occurrence. The apparent motion of a single light observed in the dark, either in the laboratory or in the air, is difficult to distinguish from real movement and is not subject to voluntary control.

The object appears to drift, now in one direction and then in another, for more than half of the time. However, certain factors tend to decrease or eliminate the phenomenon.

They are: factors which improve the spatial localization of objects, such as increasing the number of lights on a plane, rapid relative motion of the target, such as when another plane passes on a crossing course; the temporary shifting of attention from a given target for more than 10 seconds; and the dependence upon flight instruments for proper orientation. Thus, autokinetic illusions can be avoided.

Another approach to the problem was made in an investigation of nystagmic eye movements of the subject and the apparent motion and displacement of visual targets that follow violent rotation. Graybiel[3] has named this visual illusion the "oculo-gyral illusion" because it occurs following rotary stimulation of the semicircular canals.

Although considerable study had been made of the variability of vestibular nystagmus, its magnitude, duration, phases, and other aspects, by Bárány, Dodge, Dusser de Barenne and de Kleijn, Holsopple and others, Graybiel, *et al.* attempted to measure the magnitude and duration of the illusion and to relate it in a systematic way to the conditions of stimulation of the subject.

Several experiments were conducted upon human subjects in the rotating Link trainer and the human centrifuge. The principal variables introduced were the illumination, both general and that of the target, the direc-

* From the U. S. Naval School of Aviation Medicine, Naval Air Station.

tion and intensity of the stimulus, and the position of the head of the subject.

The results of these experiments show that, in a lighted room, relatively strong vestibular stimulation is required before visual illusory effects are noted. In the dark, however, the threshold for apparent motion

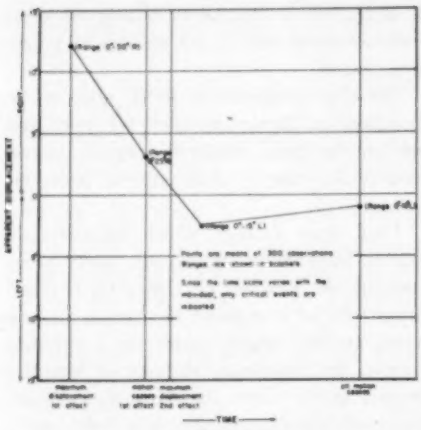

Fig. 1 (Imus, Graybiel, Brown, and Niven). Means and ranges of apparent displacement of a fixed visual target following rotation of subjects to the left in a Link trainer

is as small as 0.2 to 0.3 degrees of rotary acceleration per second per second.

Measurements in the dark are complicated by the autokinetic illusion when the target is a single light. This complication was removed by using a three-dimensional target, consisting of a box with illuminated borders.

When relatively strong stimulation is used, as, for example, the sudden cessation of rotation following 20 revolutions of the subject at 25 r.p.m., a series of illusory effects are obtained. The target moves rapidly in a direction opposite to the recent rotation for 30 to 40 seconds, followed by a second apparent motion in the opposite direction of nearly the same duration. In some instances a third apparent motion in the same direction as the first may be observed for a few seconds.

By inducing an after-image of a vertical filament in the eyes before rotation, it can be demonstrated that these apparent motions are due to nystagmic eye movements. Following cessation of rotation, the after-image always seems to move in a direction opposite to that of the image of the illuminated box which is presented now for purposes of comparison.

In order to investigate whether aviators become adapted to the effects of the gyrations of aircraft, and to determine the relationship between apparent displacement and apparent motion, further laboratory experiments[4,5] were undertaken.

In one of these experiments, 12 subjects were rotated in a Link trainer five times per day for 10 days. In each trial they were rotated at 26 r.p.m., for one minute and then decelerated rapidly to a complete stop. During and after rotation the subject's head was maintained at a fixed 15-degree forward inclination.

Reports upon the location of the target indicate a general tendency to localize it in the direction of the apparent motion. Figure 1 represents this trend.

When rotation stops, the target is localized to the right in the direction of initial apparent motion, and remains somewhat displaced even after the motion ceases. With onset of apparent motion to the left, there is some displacement to the left which persists until the cessation of the apparent motion, and sometimes longer.

In general, then, some subjects, but not all, localize the target off-center and in the direction of its apparent movement. Individual and group differences are marked. The subject's knowledge that the target actually is straight ahead and the amount of his past experience in the situation, especially, produce discrepancies between individuals.

Table 1 presents the range and direction of maximum displacement of the visual target following rotation of the subjects to the left in the Link trainer.

After rotation, 11 of the 12 subjects localized the target immediately in the direction of the first apparent motion and six reported

displacement in the same direction at the moment the apparent motion ceased.

The amount of apparent displacement varied greatly between subjects and between trials. Four observers reported displacements ranging from 15 to 50 degrees; whereas, eight other observers generally reported little or no displacement immediately following rotation. Only six of the observers reported slight displacements at the time the apparent motion to the right ceased and only four of them reported displacement at the time all apparent motion had finally ceased.

For those who experienced apparent displacement of the target, the displacement persisted a few seconds after all well-defined apparent motion had ceased. Whenever displacement was reported it always occurred in the direction of apparent motion, either in the first or the second effects.

A partial check on the role of nystagmus in controlling displacement following rotation is provided by independent records of duration of nystagmus. After the observations in the Link trainer were completed, each subject was rotated 10 times in 20 seconds on a Bárány chair. Using stop-watches, two observers noted the duration of nystagmus on three such tests.

The medians of the combined sets of observations are presented in Table 2 and are compared with the mean duration of apparent motion and apparent displacement obtained in the Link trainer.

It is not surprising that individuals with long-lasting nystagmus also report cessation of apparent motion only after correspondingly long periods (rho = +0.80). Among the factors precluding a perfect correspondence is the difficulty of judging visually the cessation of nystagmus. That judgments of displacement are also controlled, in part, by nystagmus is indicated by the relation between their durations (rho = +0.57). Individuals with long-lasting nystagmus tend to report the target as located to the right for correspondingly long periods.

The relationship between apparent motion and apparent displacement is indicated by a rho of +0.73. These rhos were calculated from the data of Table 2.

During his 10 daily sessions each subject had five trials in which he reported on apparent motion or location of target. The effects of adaptation within the group of trials are of interest. Figure 2 presents the general trend in terms of the mean of the 60 determinations for each trial. It may be noted

TABLE 1

APPARENT DISPLACEMENT OF VISUAL TARGET FOLLOWING ROTATION OF SUBJECTS TO THE LEFT IN A LINK TRAINER

Subject	Range and Direction of Maximum Displacement			
	During First Effect	At End of First Effect	During Second Effect	At End of Apparent Motion
Group I				
R. S.	30°R–50°R	5°R	5°R–15°L	5°L
R. B.	5°R–15°R	0°–5°R	0° – 5°L	0°
B. P.	10°R–30°R	0°	0°	0°
G. R.	5°R–10°R	0°	0°	0°
H. H.	5°R	0°–5°R	0° – 5°L	0°– 5°L
A. G.	30°R–35°R	5°–25°R	0° –10°L	0°–10°L
Group II				
G. P.	15°R–35°R	5°R–15°R	0° –10°L	0°–5°L
J. H.	5°R–20°R	5°R–10°R	0°	0°
S. R.	0° – 5°R	0°	0°	0°
A. P.	0° – 5°R	0°	0°	0°
A. M.	0° – 5°R	0°	0°	0°
B. F.	0°	0°	0°	0°

TABLE 2

MEDIAN DURATION OF NYSTAGMUS FOLLOWING ROTATION IN BÁRÁNY CHAIR COMPARED WITH MEAN DURATION AND DISPLACEMENT OF A VISUAL TARGET FOLLOWING ROTATION (OF SUBJECTS TO THE LEFT) IN A LINK TRAINER

Subject	Median Duration of Nystagmus (seconds)	Mean Duration of Movement (seconds)	Mean Duration of Displacement (seconds)
Group I			
R. S.	18.5	34.7	46.4
R. B.	13.5	25.0	25.4
B. P.	12.5	27.7	54.0
G. R.	16.5	29.9	29.8
H. H.	12.5	25.3	50.2
A. G.	19	30.1	40.0
Group II			
G. P.	14.5	22.4	23.2
J. H.	9.5	2.6	15.0
S. R.	13.5	31.8	28.1
A. P.	8	13.7	13.6
A. M.	10.5	22.8	9.7
B. F.	10	21.3	0

that there is little change from trial to trial.

The effects of repeated bodily rotation are also shown in a comparison of results obtained for the five daily sessions. Figure 3 presents the mean of 60 determinations for each day. It may be noted that there is no apparent effect of one day's rotation upon reports of apparent motion or displacement the next day. These results agree with the more extensive findings of Graybiel and Hupp[9] and Clark and MacCorquodale.[10]

The results of the above experiment may be summarized as follows:

The subjective alterations of a visual target with respect to velocity and position as observed after rotation are not related in a consistent fashion from observer to observer, nor are the changes consistent with those to be expected from analysis of velocity and displacement characteristics of a target in real motion.

Following rotation to the left, the visual target, actually straight ahead, appears to move rapidly to the right and is localized in the direction of its apparent movement.

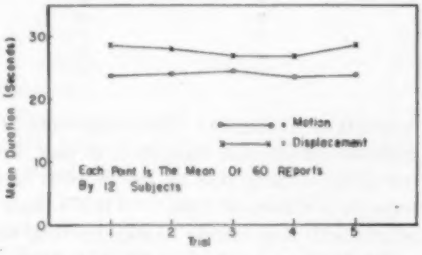

Fig. 2 (Imus, Graybiel, Brown, and Niven). Showing variations in judgments of apparent motion and displacement by trial.

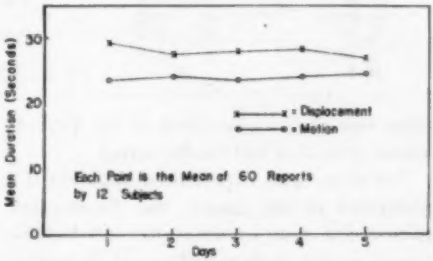

Fig. 3 (Imus, Graybiel, Brown, and Niven). Showing variation in judgments of apparent motion and displacement by days.

However, there are significant differences between individuals in magnitude of displacement of target as well as in duration of apparent motion and displacement.

Individuals with long-lasting nystagmus in general observe apparent motion and displacement over more extended periods of time.

There was no systematic variation from

trial to trial, or day to day, in the judgments of either apparent motion, or apparent displacement, to indicate that the subjects were becoming habituated to rotation.

During experiments conducted on the human centrifuge[6] another type of visual illusion was discovered. Graybiel calls it the "oculo-gravic" illusion, because it is induced by accelerative forces acting upon the otolith organ, which forces are measured in gravitational units.

A review of the literature showed that Brower, in 1875, had distinguished between the otolith organs, which respond to the position of the head in space (gravitational effect), and the semicircular canals, which respond to rotation of the head in one of the three principal planes (change in velocity).

The "oculo-gravic" illusion provided still another means of studying orientation. Using an infinity target for visual fixation, and with the head held firmly in the primary position while the subject faces the center of the centrifuge, changes in the centrifugal forces produce marked changes in the apparent position of the visual target.[7]

As the centrifuge is accelerated slowly in the dark, the image of a horizontal line in the infinity target, which is mounted directly in front of the subject's eyes, appears to rise until it is estimated to be 45 degrees above the horizon. When the rate of revolution of the centrifuge becomes constant, the target appears to remain fixed for that particular speed of revolution. Meanwhile, the subject, who is strapped erect in a chair, feels himself gradually tilted backward until he feels as though he were lying on his back and looking up at the target.

When the power is cut off and the centrifuge coasts to a stop, the subject reports that the target gradually returns to its true position and he soon feels that he is sitting erect. The apparent position of the image throughout the experiment seems to be in line with the resultant of the gravitational and centrifugal forces acting upon the otolith organ.

A series of experiments[8] was undertaken in the human centrifuge in order to determine the quantitative relationship obtaining between the resultant of centrifugal and gravitational forces acting upon the subject and his perception of the visual vertical when no visual frame of reference was present.

Using the psychophysical method of average error, the subjects were required to adjust a luminous collimated line until, to them, it appeared to be vertical. Adjustments were made under stationary conditions, and during eight different angular velocities ranging from four r.p.m. to 11 r.p.m.

It was found that the visual vertical varies directly with the angle of the resultant force. Individual differences occur in both constant and variable errors, but the combined data of these experiments, based upon 480 adjustments, indicate a relatively accurate perception of the visual vertical (mean, constant error $= -0.38°$, $\sigma = 1.30°$). Individual differences increase with increasing angular velocity.

It was concluded from these experiments that Mach's hypothesis, which states that subjects adjust the visual vertical in accordance with the resultant of centrifugal and gravitational forces, is supported. Furthermore, these experiments indicate that, without a visual frame of reference, bodily orientation is dependent primarily upon postural factors.

The experiments in the human centrifuge led to further empirical tests in flight. The experiments described in three reports[9] were conducted in the rear cockpit of an SNJ-6 aircraft, using a fixed collimated "star" as the visual target. The observer recorded his observations on a wire recorder.

The results show that illusions of motion and displacement of the visual target may occur during all degrees of bank from 10 degrees to 60 degrees, and always occurred during banks of 40 degrees and above. Although there are marked individual differences between subjects, there is a direct relation between the degree of bank and

the amount of apparent motion and displacement observed. When two methods of executing a banking maneuver are compared no significant differences in the illusory phenomena are observed.

These two methods are described as follows: (1) Executing a turn with constant power setting and changing the angle of attack of the wing to maintain proper altitude; (2) executing a turn by holding the angle of attack constant and increasing power to maintain altitude.

In the first case, there is a definite change in the magnitude and direction of the accelerative forces acting upon the subject. In the second case there is a change in the magnitude of the forces without a change in direction. It is apparent that repeated maneuvers do not lessen the effects; therefore, it is safe to assume that habituation does not occur.

In order to verify this assumption experimentally, three subjects were rotated in the Link trainer for 14 days for an average of approximately 20 successive runs per day. No evidence of habituation appeared in the data. This report[10] states that the oculogyral illusion can be expected to occur at night in pilots of aircraft when accelerations above threshold are present. This lack of habituation appears to be true in spite of extensive flight experience of the pilot.

Summary

Unusual aircraft accidents led to a long series of experiments on visual illusions which were thought to affect pilots in operating aircraft at night or under adverse conditions of visibility and weather.

A survey of experienced aviators revealed that such illusions were relatively frequent in occurrence.

Experiments on the autokinetic illusion indicated that this type of illusion could occur in night flying and could be controlled by increasing the number of formation lights on the planes, and by instructing pilots to shift their gaze.

Experiments in a Bárány chair, a rotating Link trainer, and the human centrifuge indicated that acceleration and deceleration forces produce illusions of motion and displacement of visual targets. Other experiments on the human centrifuge show that gravitational forces cause apparent displacement of visual targets and illusions of changes in bodily position. These experiments were confirmed by flights in a Naval training aircraft.

Repeated experiments, both in the laboratory and in flight, show that the illusions persist, and that the subjects do not become adapted to the illusory effects.

Conclusion

For a period of five years, a series of experiments have been conducted on the subject of orientation in space. The results have shown that hazards of flying are increased by illusions to which all pilots are susceptible. For example, it has been shown, beyond all doubt, that a pilot, when flying at night or in fog, cannot tell whether he is in a climbing turn or in a diving turn. It is important, therefore, to explain the nature and cause of these illusions.

Pilots should be convinced that they must rely upon the instruments in their plane. They must learn to ignore their bodily sensations, no matter how overpowering the latter may be. Much of the fear and mystery involved in spatial disorientation are removed when pilots understand the cause of these illusions and how to counteract them.

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SEX-LINKED OCULAR ALBINISM DISPLAYING TYPICAL FUNDUS CHANGES IN THE FEMALE HETEROZYGOTE*

HAROLD F. FALLS, M.D.
Ann Arbor, Michigan

Albinism has strikingly ever stimulated the curiosity of man both in antiquity and modern time. Most ophthalmologists have an intimate acquaintanceship with the eye in universal albinism but are not as versed with the ocular changes in (1) incomplete universal albinism and (2) albinism of the eye alone.

This latter type of incomplete albinism, wherein the pigmentary deficiency is limited to or occurs mainly in the eyes, was first recognized by Nettleship.[1] This author also demonstrated that the disease was sex-linked recessive in its inheritance.

Such changes as fundus albinism, hypoplasia of the macula, head nodding, nystagmus, and amblyopia are most commonly encountered in the affected male patient. The iris may be blue or gray. Nettleship,[1] Holm,[2] Vogt,[3] Engelhard,[4] Owens,[5] Waardenburg,[6] and Papillon and Lestoquoy[7] have reported families which have demonstrated this rather rare ocular anomaly.

It has been my privilege to study two families of this sex-linked ocular albinism in which the heterozygous or carrier female presented a clinically detectable and constantly uniform funduscopic picture. This heterozygous fundus picture has heretofore been unrecognized with but one possible exception.

Vogt,[8] in discussing "The iris in albinismus solum bulbi," spoke of the fundus of Emma B. as follows: "Peripheral retinal pigment stippling, dark and light patches alternate, giving a salt and pepper appearance, sometimes mottled in bigger patches and striped." He did not describe other female carrier fundi and he evidently failed to recognize the significance of the described changes

* From the Department of Ophthalmology of the University Hospital and the Heredity Clinic Laboratory of Vertebrate Biology, University of Michigan. Support for this study was provided by the board of governors of the Horace H. Rackham School of Graduate Studies, University of Michigan.

which so closely approximate the retinal alterations seen in the fundi of the carrier females in my two families.

Method of Study

Kindred 976 (fig. 1) was first encountered on November 30, 1946, at the Wayne General Hospital where I was requested to explain the patient's (VI-1) horizontal nystagmus and head nodding. A study of the family was instigated when the child's mother volunteered that her father was similarly affected.

As complete as possible ophthalmic examinations were performed either in the home, clinic, or institution, depending upon the coöperation of the various individuals. The normal, as well as the apparently affected individuals, were examined.

All persons examined, with the exception of very young children, were tested for defects in color vision by means of Ishihara plates. When feasible, retinoscopy under cycloplegia was performed. The medical illustrator made many of her preliminary sketches in the homes and frequently under most adverse circumstances. Confrontation fields were performed when more accurate Bjerrum or perimetric studies were not feasible. Red-free light studies were performed with the binocular ophthalmoscope and it is freely admitted that we are not satisfied with the quality of the filter.

When the nature of the female heterozygous state was once recognized, it was recalled that I had long had under observation a family similar in all respects to the above, Kindred 420 (fig. 3). This family was then restudied.

The spouses of the subjects of this study were examined in almost all cases and were found to be normal with respect to the trait being studied. These spouses have, therefore, been omitted from the pedigree. Consanguinity was ruled out insofar as amnestic data permitted.

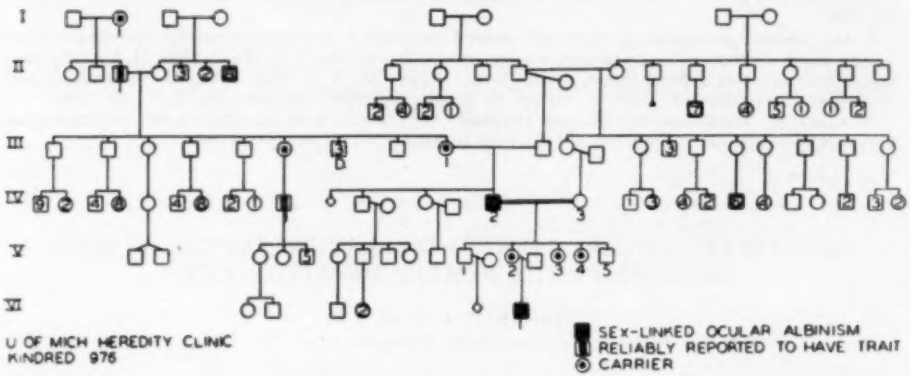

Fig. 1 (Falls). Pedigree of Kindred 976.

In the following sections of the paper each individual member will be identified by means of a double number. The Roman numeral will indicate the generation and the Arabic numeral the position occupied by that individual in the designated generation. For example, the propositus in Kindred 976 becomes VI-6 (fig. 1).

Description of Ocular Findings of Affected Individuals

Kindred 976 (fig. 1)

This family came from Tennessee and only a limited few were available for study. The pedigree is incomplete and it is hoped to be able to extend it more accurately if cer-

tain prejudices can be overcome in the future.

(II-1). This deceased minister of the gospel was known to all as "dancey-eyed." His daughter, our informant, recalled that his eyes were very blue, that they danced about and that his visual acuity was very poor especially in the bright sunlight. He could read if the print was held fairly close to his eyes. His hair was sandy in color. This man was an extremely emotional individual.

(III-1). This quiet, well-mannered, 68-year-old woman presented graying sandy hair. She maintained that she had always enjoyed good visual acuity other than for the need of reading glasses. Her corrected visual acuity was 6/6—2, O.U. The skin was tan and the eyelashes and eyebrows were sandy brown color.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The ocular motility was normal. A minimal degree of blepharochalasis was present, O.U. The conjunctiva, cornea, anterior chamber and iris were normal, except for arcus senilis, O.U. The irises were light blue with considerable golden-brown pigmentation superimposed in the stroma in and about the pupillary border and sphincter area. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were clear, except for a few fine floating vitreous opacities. The disc was oval vertically, of good color, and presented a small physiologic depression. The disc pigment ring was incomplete. The macular area presented pigment stippling and sparseness with an apparently good foveal reflex. The retinal arterioles presented increased reflex striping, A-V notching, and an irregularity in caliber. The retinal pigment within only a few degrees of the foveal area became clumped into small clusters or nests of coarse, cocoa-brown granules. The choroidal vasculature throughout the entire periphery was normal.

The left eye was the same as the right (fig. 2). Color vision was normal. Ocular tension was: O.D., 22 mm. Hg; O.S., 24 mm. Hg (new-Schiøtz). Gross confrontation field was normal.

Diagnosis. Typical female-carrier state of sex-linked ocular albinism.

(IV-2). This short, thin, wiry male was an inmate of the local state institution for the insane. A diagnosis of manic-depressive psychosis was tentative. The patient's skin pigmentation was normal. The hair was light brown, but this had been much more blond earlier in life. The corrected visual acuity was 6/30—1, O.U. He could read newspaper print if he held it sufficiently close to his eyes. Head nodding in infancy was recalled by his parents.

Ophthalmic Examination

External examination. There were several degrees of alternating divergent strabismus. The ocular motility was within normal limits. The near point of convergence was remote. There was present a coarse, pendular, irregular nystagmus which became exaggerated upon monocular fixation. The conjunctiva, cornea, anterior chamber, and iris were normal. The iris was a light blue with golden-brown pigment superimposed in and about the pupillary border. The pupillary reflexes were prompt and equal. The iris was of apparently normal structure, yet transmitted light on scleral transillumination.

Funduscopic examination. O.D., the lens and central media were clear. The optic-nerve disc was normal, except for moderate situs inversus vasorum. The macular area was much pinker than the surrounding retina and the choroidal vasculature was less conspicuous in this central area. No foveal reflex could be seen. The choroidal vascular network was easily seen throughout the entire retina and nowhere could any retinal pigmentation be seen.

The left eye was the same as the right (fig. 2). Color vision was normal. Visual fields could not be taken; nor could retinoscopy be performed.

Diagnoses. Sex-linked ocular albinism; amblyopia; nystagmus.

(V-2). An asthenic, young, reddish-blond divorcee who was most coöperative. She claimed she, at times, developed headaches with exposure to bright sunlight but suffered no other indication of light intolerance. Her uncorrected visual acuity was 6/12, O.D., and 6/9—2, O.S.

Ophthalmic Examination

External examination. The eyes were straight in the primary position with minimal divergence under cover. The ocular motility was normal. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were hazel blue with much brown pigment superimposed especially about the pupillary border. The pupillary reflexes were prompt and equal, O.U.

Funduscopic examination. O.D., the lens, central media, and the optic-nerve disc were normal. The retinal vasculature was normal in distribution and ratio. The macular area was characterized by the presence of stippled, cocoa-brown pigmentation. Within a few degrees of the fovea the choroidal vasculature became easily seen and the retinal pigment grew very sparse. This was grouped in small nests and clusters. The individual pigment granule seemed large and angular (fig. 2).

The left eye was the same as the right. Color vision was normal. Bjerrum field was normal. Refraction (cycloplegia): O.D., +0.75D. sph. ⌒ +1.0D. cyl. ax. 32° = 6/6—1; O.S., +0.75D. sph. ⌒ +1.0D. cyl. ax. 148° = 6/6.

Diagnosis. Female-carrier state of sex-linked ocular albinism.

(V-3). An auburn haired, well proportioned, 14-year-old girl who presented normal skin pigmentation with freckles. She was alert and coöperative. The uncorrected visual acuity was: 6/7—2, O.D.; 6/7—1, O.S.

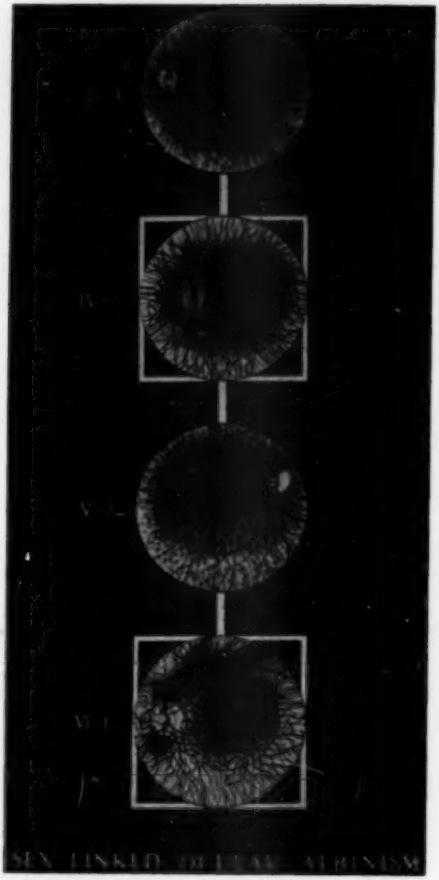

Fig. 2 (Falls). Fundus findings in four members of Kindred 976.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The ocular motility was normal with divergence under cover. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were hazel, a blue background with superimposed brown pigmentation. A few pigment iris freckles were present. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens were clear as was the vitreous. The disc was normal in color, size, and shape. A cilioretinal artery was present at the 8-o'clock position, O.D., and the 3-o'clock position, O.S. The macular area pigment was quite sparse and appeared as if stippled. The foveal reflex could be seen despite the vividness of the choroidal vasculature.

As one left the region of the macular area, the choroidal vessels appeared to be seen more easily. The retinal pigment was grouped into small clusters of cocoa-brown, angular granules. This pigment was practically absent in the extreme periphery. The retinal vessels were normal.

The left eye was the same as the right. Color vision was normal. Confrontation field was normal.

Diagnosis. Sex-linked ocular albinism—female-carrier state.

(V-4). This attractive, 13-year-old, slightly auburn-haired girl had no ocular complaints. There was excellent coöperation. The skin pigmentation was normal with freckles. The uncorrected visual acuity was 6/6—2, O.U.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The ocular motility was normal. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were hazel in color, a blue with much brown in the stroma. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were normal. The disc was normal in size, shape, and color. There was an incomplete pigment ring about the disc. An excellent foveal reflex was present. The macular retinal pigment was scant and stippled. As one approached the periphery, this pigment became more scant, being arranged in clusters or small, linear rows. This exposed vividly an apparently normal choroidal circulation. The pigment granules seemed angular and were chocolate brown in color.

The left eye was the same as the right. Confrontation field was normal. Color vision was normal.

Diagnosis. Sex-linked ocular albinism—female-carrier state.

(VI-1). When examined on November 30, 1946, this seven-month-old male baby, the propositus of this study, presented rather light blond hair. The child was normal physically and was seemingly developing normally. The skin pigmentation was not unusual.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The gross ocular motility was normal. There was an irregular to-and-fro nodding of the head which became accentuated when the child was irritated. There was a coarse, pendular nystagmus having a rotatory component. Monocular fixation would exaggerate the amplitude and rapidity of the excursions.

The near point of convergence was normal. The pupillary reflexes were prompt and equal. The irises were a very light blue, with some gray and brown flecks present near the pupillary border. Transillumination of the sclera emitted light through the iris stroma. The conjunctiva, cornea, anterior

chamber, and iris were normal. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were clear. The disc was considered within normal limits. The retinal vasculature was normal in distribution and appearance. The foveal reflex was absent. The choroidal vasculature was sharply seen throughout the entire fundus. The macular area presented a pinkish glow which was absent elsewhere.

The left eye was the same as the right (fig. 2). Confrontation fields were not done. Color vision was not done.

(III-1). This 33-year-old woman, the mother of the propositus, had no specific ocular complaint. The hair was light brown, as were the eyelashes and eyebrows. The skin was possessed of normal pigmentation and the patient tanned easily. The uncorrected visual acuity was 6/15—2, O.D., and 6/12—1, O.S.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The ocular motility was normal with minimal divergence under cover. The conjunctiva, cornea, anterior chamber, and iris were

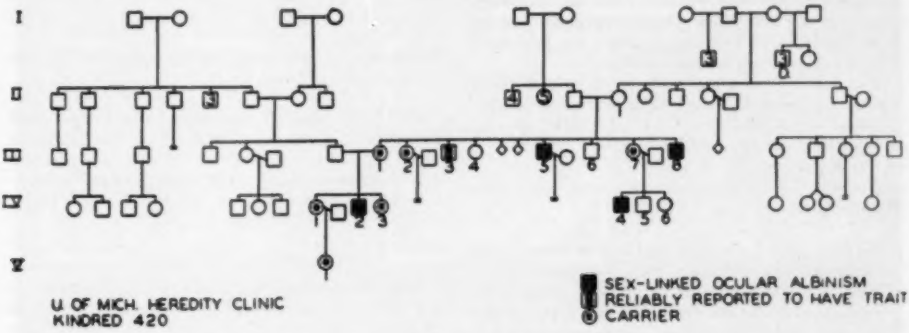

Fig. 3 (Falls). Pedigree of Kindred 420.

Diagnosis. Sex-linked ocular albinism.

Reëxamination on July 26, 1949, revealed a complete absence of head nodding and the nystagmus was much less conspicuous. The irises were a darker blue with much more brown superimposed. They still transmitted light. There was no appreciable change in the funduscopic appearance, O.U.

Cycloplegic refraction: O.D., +4.25D. sph. ⊃ +2.75D. cyl. ax. 90° = 6/60+1 (E chart); O.S.; +4.25D. sph. ⊃ +2.75D. cyl. ax. 90° = 6/60+1 (E chart.

KINDRED 420 (fig. 3)

This southwestern Michigan family was first encountered as a result of the visit of the propositus (IV-2) to the Ophthalmology Clinic of the University of Michigan Hospital on August 17, 1943.

(II-1). This woman was never examined ophthalmoscopically, but did serve as an informant, aiding greatly in obtaining data concerning the family. Her visual acuity was sufficiently satisfactory to permit her to read and write without discomfort. She had a moderate photophobia in bright sunlight. She died of carcinomatoses before I could examine her.

normal. The irises were light blue with some golden-brown in the stroma near the pupillary border. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were negative. The disc was oval vertically and normal in size and color. The macular area exhibited an excellent foveal reflex. The macular region presented stippled pigmentation throughout. This pigment was coarse and was arranged in small groups. This grouping became more conspicuous as the pigment granules became more sparse in the midcentral and peripheral retina. In fact, it suggested an unusual form of grouped pigmentation of the retina. The choroidal vasculature was easily seen throughout the fundus.

The left eye was the same as the right (fig. 4). Color vision was normal. Refraction (diagnostic): O.D., +3.25D. sph. ⊃ +1.25D. cyl. ax. 42° = 6/6—1; O.S., +4.12D. sph. ⊃ +0.75D. cyl. ax. 168° = 6/6—1. In red-free light there was yellow color in the macular area.

Diagnosis. Female-carrier state—sex-linked ocular albinism.

(III-2). This 41-year-old woman presented dark, brownish hair, eyebrows, and eyelashes. She had no specific ocular complaints. Her uncorrected visual acuity was 6/9—3, O.D., and 6/12+1, O.S.

Ophthalmic Examination

External examination. The eyes were straight in the primary position with considerable lateral deviation under cover. The ocular motility was normal. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were light blue with some gray superimposed in and about the pupillary border. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were clear. The optic-nerve disc was of normal color, size, and shape. The macular area presented a good foveal reflex. The choroidal circulation was easily seen through scattered islands of cocoa-brown pigment granules a few disc diameters from the macula. These pigment granules became less numerous as one approached the periphery. The retinal vasculature was normal.

The left eye was the same as the right. Color vision was normal. Visual fields were normal. Refraction (cycloplegia): O.D., +0.25D. sph. ⊂ +1.0D. cyl. ax. 26° = 6/6; O.S., +0.25D. sph. ⊂ −1.25D. cyl. ax. 70° = 6/6.

Diagnosis. Female-carrier state—sex-linked ocular albinism.

(III-3). This male child died at five years of age of pulmonary complications with a severe attack of influenza. He was interpreted as being reliably reported to have had the trait. He was a very blond child with light blue irises. There was known to have been nystagmus. Head nodding in infancy was also recalled.

III-5. This light, brown-haired, 31-year-old man was most coöperative and interested. He had always had mild photophobia. In early childhood he sunburned very easily, but in later years began to tan readily. Head nodding was recalled in his infancy. In his early school years he was regarded as mentally retarded, but it is interesting to read the report of the psychologist: "The I.Q. is 84, a dull normal. I suspect this child's training has been neglected and his environment poor." His uncorrected visual acuity was 6/30, O.U.

Ophthalmic Examination

External examination. There were 20 to 25 degrees of alternating divergent strabismus (Priestly-Smith). A slight ptosis was present, O.D. The patient could fix equally well, O.U. There was no convergence power. A coarse, irregular, pendular, horizontal nystagmus with an inconstant rotatory component was observed. This became accentuated upon forced monocular fixation.

The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were light blue with gray superimposed. The irises transmitted scleral light.

Funduscopic examination. O.D., the lens and vitreous were clear. The disc was irregular, small, and the margins indistinct. There was high central branching of the central retinal artery and veins. The macular area was much more pink than the surrounding retina and there was no foveal reflex present. In addition, the pink background extended out along the retinal vessels for several disc diameters from the disc. With unsatisfactory red-free light there was no evidence of macular yellow color. A small choroidal nevus was seen four disc diameters from the disc in the 1-o'clock meridian.

The left eye was the same as the right. No choroidal nevi were seen. Color vision was normal. Visual-field studies showed a central scotoma with a 1/1,000 red test object.

Cycloplegic refraction. O.D. −0.75D. sph. ⊂ +1.0D. cyl. ax. 124° = 6/30+1; O.S., −0.25D. sph. ⊂ + 3.0D. cyl. ax. 130° = 6/30. Kollmorgen telescopic unit (2 by 2): O.D. = 6/15; O.S. = 6/30 +2.

Diagnoses. Sex-linked ocular albinism; ocular nystagmus; amblyopia.

(III-7). This 26-year-old woman presented rather dark brown hair, but her skin was fair with many freckles. She had no specific ocular complaints. She exhibited no specific physical deformity. The patient's uncorrected visual acuity was: O.D., 6/9−1; O.S., 6/9−2.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The ocular motility was normal. There was convergence under cover. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were blue with brown pigmentation of the stroma in and about the pupillary opening. The iris did not emit light to scleral transillumination of the globe.

Funduscopic examination. O.D., the lens and central media were clear. The disc was oval vertically and of good color. The margins were indistinct. The retinal vasculature was normal. The macular area and midcentral retina exhibited large granules of golden-brown pigment scattered in small groups. The pigmentation of the retinal periphery was very sparse. The choroidal vessels were easily seen throughout the entire fundus, with the exception of the macular area. The retinal vessels were normal.

The left eye was the same as the right (fig. 4). Color vision was normal. Visual fields showed minute contracture of peripheral perimetric field.

Cycloplegic refraction. O.D., +2.25D. sph. ⊂ 0.0D. cyl. ax. 0° = 6/6−3; O.S., +0.25D. sph. ⊂ +0.25D. cyl. ax. 145° = 6/6−2.

Diagnosis. Female carrier state of sex-linked ocular albinism.

(III-8). A sandy haired and freckle skinned, 24-year-old man presented a prosthesis, O.D. He stated that the right eye had been very small at birth and it had been enucleated four years prior to the present date of examination. He appeared quite sound physically and has always been considerably much of a wayfarer. His uncorrected visual acuity was 6/9+4, O.S.

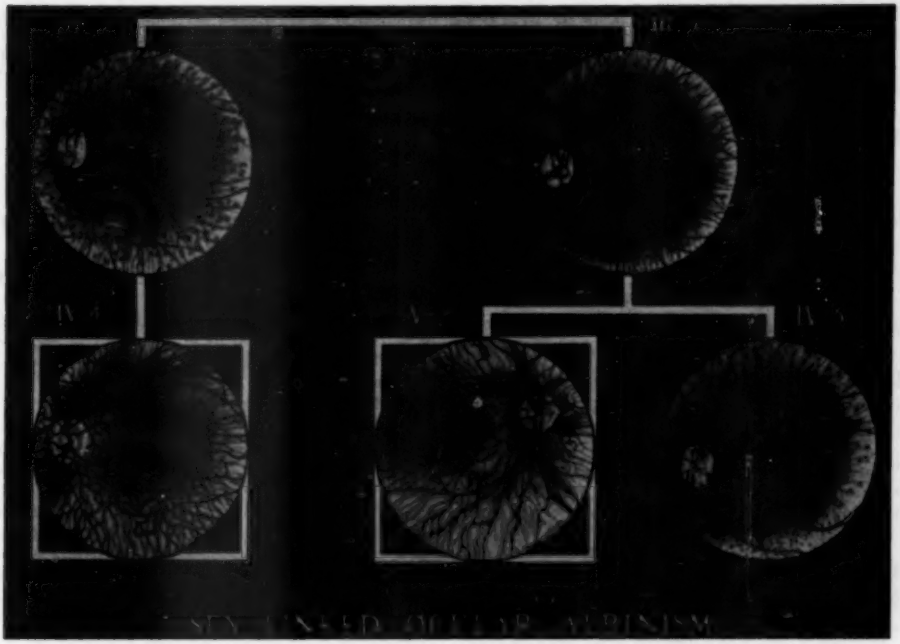

Fig. 4 (Falls). Fundus findings in five members of Kindred 420.

Ophthalmic Examination

External examination. O.D., prosthesis. O.S., there was a fine, rapid, horizontal nystagmus which increased in amplitude when the eye was directed to the extremes of gaze. A very slight rotatory component was present. The conjunctiva, cornea, anterior chamber, and iris were normal. The iris was light blue in color. Transillumination was very faintly possible. The pupillary reflex was prompt.

Funduscopic examination. O.D., prosthesis. O.S., the central media was clear. The disc was irregular in shape and there was an incomplete pigment ring. The macular area revealed considerable visible pigmentation. The foveal reflex was not seen. The extreme retinal periphery revealed the choroidal circulation vividly as there was an almost complete lack of pigmentation. A brown-pinkish retinal color extended out along the various retinal vessels There was definite retinal pigmentation present and the fundus picture very closely approached that of the female heterozygote. Color vision was normal. Central visual field was normal.

Cycloplegic refraction. O.S., +3.25D. sph. ⊃ +0.25D. cyl. ax. 2° = 6/6—1.

Diagnoses. Mild degree of sex-linked ocular albinism; nystagmus; prosthesis.

(IV-1). This 20-year-old woman presented light brown hair. She stated that she had been quite blond earlier in life. She still freckled easily with sun exposure. She was well developed and proportioned, displaying no gross physical pathologic condition. The uncorrected visual acuity was 6/6—2, O.D., and 6/6—1, O.S.

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The ocular motility was normal. A slight ptosis was present, O.D. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were blue with considerable gray present in the stroma. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were clear. The disc was oval vertically, of good color with high central branching. The margins were slightly indistinct. The foveal reflex was seen. A few degrees from the macular area, in any direction, there appeared to be almost complete absence of the retinal pigment except for small clusters of coarse, cocoa-brown granules. The retinal vasculature was normal. The choroidal vessels were very clearly seen.

The left eye was the same as the right. Color vision was normal. Visual fields showed peripheral contraction minimal.

Cycloplegic refraction (August 30, 1943). O.D., +2.75D. sph. ⊃ +1.0D. cyl. ax. 120° =6/9—2;

O.S., +3.0D. sph. ⊃ +0.75D. cyl. ax. 60° = 6/9—2. On August 7, 1949: O.D. +1.5D. sph. ⊃ +0.37D. cyl. ax. 110° = 6/6—1; O.S., +1.75D. sph. ⊃ +0.37D. cyl. ax. 70° = 6/6—1.

Diagnosis. Female-carrier state of sex-linked ocular albinism.

(IV-2). This blond, chubby boy, the propositus of this study, was first seen on August 17, 1948, at the Ophthalmology Clinic at the University of Michigan Hospital. There were no physical defects. The skin presented normal pigmentation. The uncorrected visual acuity was 6/60, O.U.

Ophthalmic Examination

External examination. The eyes were straight. There was a coarse, pendular nystagmus which was exaggerated by monocular fixation. A rotatory component was also noted. The ocular motility was normal. The conjunctiva, cornea, anterior chamber, and iris were devoid of pathology. The pupils were slightly ectopic, down and in. There was a good convergence near point. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were clear. The disc was slightly irregular in shape. The foveal reflex was absent. The macular area was pink, but no gross pigmentation could be seen. The retinal vasculature was normal. The choroidal vasculature was vividly seen throughout the entire fundus (fig. 4).

The left eye was the same as the right. Color vision was normal. Visual fields showed a small central scotoma with red 1/1,000, but could not be outlined.

Cycloplegic refraction. O.D. +2.5D. sph. ⊃ +1.5D. cyl. ax. 100° = 6/30; O.S., +2.5D. sph. ⊃ +2.0D. cyl. ax. 80° = 6/30.

Diagnoses. Sex-linked ocular albinism; ocular nystagmus; amblyopia.

(IV-3). A rather fleshy 12-year-old, muddy blond girl had no specific ocular complaint. Her physical examination presented no gross physical abnormality. The skin was freckled in the exposed parts. The uncorrected visual acuity was 6/9+2, O.U.

Ophthalmic Examination

External examination. The eyes were straight in the primary position with lateral deviation under cover. The ocular motility was normal. The conjunctiva, cornea, anterior chamber, and iris were normal. The irises were a light, powder blue with much gray in the stroma. Transillumination of the sclera emitted light faintly through the iris periphery. The pupillary reflexes were prompt and equal.

Funduscopic examination. O.D., the lens and central media were clear. The disc was normal in size, shape, and color. The macular area presented a foveal reflex. Red-free light disclosed normal macular yellow coloration. The macular retinal pigment was stippled, cocoa-brown in color, and very sparse. The same pigmentation became more scant as the retinal periphery was approached. It was arranged in isolated nests or clumps. An occasional linear row was observed. The retinal vasculature was normal. The choroidal vessels were easily and clearly seen.

The left eye was the same as the right (fig. 4). Color vision was normal. Visual fields showed a slight peripheral contraction.

Cycloplegic refraction. O.D., +1.25D. sph. ⊃ 0.0D. cyl. ax. 0° = 6/6—2; O.S., +1.25D. sph. ⊃ +0.25D. cyl. ax. 165° = 6/9+3.

Diagnosis. Female-carrier state (heterozygote) sex-linked ocular albinism.

(IV-4). This five-and-a-half-year-old, light blond boy has had poor eyes since birth. The physical examination was normal for any gross pathologic condition. The skin was of normal color or slightly pale. The uncorrected visual acuity was 6/60, O.U. (E chart).

Ophthalmic Examination

External examination. The eyes were straight in the primary position. The near point of convergence was remote. The ocular motility was normal. A coarse, horizontal nystagmus was present which was accentuated with lateral fixation. The conjunctiva, cornea, anterior chamber, and iris were negative, O.U. The irises were a light blue and they transmitted reflected light from the globes.

Funduscopic examination. O.D., the lens and central media were clear. The disc presented an irregular outline and situs inversus vasorum. The fundus was devoid of retinal pigmentation. The macular area revealed a denser pink color than the surrounding retina. No foveal reflex was seen. The choroidal vasculature was most vividly seen throughout the fundus.

The left eye was the same as the right (fig. 4). Color vision was normal. Visual fields could not be taken.

Cycloplegic refraction. O.D., +3.25D. sph. ⊃ +1.25D. cyl. ax. 75° = 6/60+1; O.S., +4.0D. sph. ⊃ +0.75D. cyl. ax. 110° = 6/60.

Diagnosis. Sex-linked ocular albinism.

(V-1). This one-and-a-half-year-old, brown-haired girl was well developed. The skin presented normal pigmentation. The child fixated light readily and followed Worth balls easily, O.U.

Ophthalmic Examination

External examination. The eyes were straight. The ocular motility was normal. The pupillary reflexes were normal. The conjunctiva, cornea, anterior chamber, and iris were negative. The irises were a light blue and did transmit reflected light.

Funduscopic examination. O.U., the lens and central media were clear. The disc was normal. The macular area and retinal periphery simulated in every respect that of her mother, IV-1, with the exception that there was less over-all pigmentation. The coöperation was too poor for special studies.

Diagnosis. Sex-linked ocular albinism—female-carrier state.

Mode of inheritance

The distribution of the affected cases in these two kindreds is such as to suggest rather obviously the presence of a sex-linked gene producing different but clinically recognizable retinal change in the two sexes. All affected males, wherein possible to determine, are sons of women exhibiting the described retinal pathologic processes. That the gene is not entirely recessive is evidenced by the presence of this clinically detectable change in the retinas of heterozygous females. A dominant sex-linked gene may be discredited in that the male change is dissimilar from that of the female and much more deleterious to the ocular physiology.

An alternative genetic hypothesis, that of an autosomal gene producing differing clinical pictures (phenotypes) in the two sexes, must be considered. In such one might anticipate affected males producing affected sons and normal daughters in equal proportions to that expected of the probability for normal sons and affected daughters.

Only one such opportunity to test this latter possibility was presented in these two kindreds. IV-2, in Kindred 976, had three daughters and two sons. Here all three girls were carriers and both sons were normal, as one would anticipate in a sex-linked transmission of the gene.

A partially sex-linked gene with differing manifestations in the two sexes might also be considered, but again the rather scant information more adequately supports the thesis of ordinary sex-linkage, the gene being located in the unpaired portion of the x-chromosome.

I support the postulation of an x-chromosome gene intermediate in its expression in the female and exhibiting its full effect when present in the single unopposed locus in the male. This is not unusual in ocular diseases in that choroideremia[9] and choroidoretinal degeneration[10] exhibit a similar mode of inheritance. Red-green color blindness and hereditary optic atrophy are also examples of sex-linked ocular anomalies which frequently manifest changes detectable in the heterozygous females.

Discussion

In albinism there is an inherited inhibition of pigment development throughout the entire body, as in universal albinism, or localized to the skin, hair, or eyes as in partial albinism. Vogt[3] recognized two types of partial albinism which were concerned with the eye: (1) Albinism of the eye alone (albinismus solum bulbi) and (2) albinism of the fundus alone (albinismus solum fundi).

Amblyopia, nystagmus, head nodding, and albinism of the eye are observed in albinism of the eye alone according to Vogt.[3] Normal pigmentation of the cilia, hair, and skin will be present. The iris permits light to pass through, the fovea is absent, and the fundus is albinotic in such cases.

The close similarity of the changes present in the affected males in the two described kindreds and those of albinism of the eye alone is evident.

Waardenburg,[6] in his monograph, deals at length with albinism, and recognizes that albinism may be partial and confined to the eyes without affecting the hair or skin color. In one of his more recent articles[11] he presented pedigree evidence that he was able to recognize heterozygotes in both the autosomal recessive albinism as well as in the x-chromosomal inherited ocular albinism. This was demonstrated in such individuals by a permeability of the iris to light on transillumination of the sclera. Thus again we have further support for the intermediate inheritance of albinism.

In the two reported families several rather consistent facts require emphasis. The head nodding appears to be a constant factor in all the affected males, but is confined to infancy. Perhaps the development of some pigmentation in the eye and also general pigmentation may influence this disappearance.

A gradual improvement in the visual acuity was observed in those carrier females observed for an adequate period of time and

the author feels that this may likewise be related to the acquisition of some greater pigmentation in the macular area. This improvement in visual acuity with acquisition of pigment in the retina and eye has also been observed in very blond and red-haired children. The visual acuity was also best in the affected males—III-5 and III-8—who had some evidence of pigment in the retina. Thus there appears to be a direct relationship between the efficiency of the visual acuity and the intensity of pigmentation.

A rather wide range of variability in the degree of retinal pigmentation exists in the carrier females and there is some evidence that this pigmentation increases with age. The affected males do not appear to have a total absence of retinal pigment. Actually there is a considerable range of variance in the amount of pigment present; for example, III-8 presented sufficient pigmentation to almost simulate the female retinal picture.

The irises in our affected cases in many instances did transmit light, but this was not a constant finding, especially in the females and older individuals. This is contrary to Waardenburg's findings.

Eugenic importance

The ability to recognize the female-carrier state of sex-linked ocular albinism as well as that of choroideremia or sex-linked choroidoretinal degeneration is of primary importance to both the ophthalmologist and the geneticist. Such a female is capable of transmitting the abnormal gene to her children in the following theoretical but mathematically accurate ratios: (1) 50 percent of her daughters and (2) 50 percent of her sons. Thus every daughter has one chance in two of being a carrier and every son one chance in two of being affected.

All ophthalmologists are urged to familiarize themselves with these clinically detectable retinal changes in the female heterozygote and to be cognizant of the important genetic information they endow.

Summary

1. Two families of sex-linked ocular albinism have been presented.

2. A female-carrier state, or heterozygote, with typical retinal change is described, it is believed, for the first time.

University Hospital.

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FLICKER FUSION FIELDS*

IV. Neuro-Ophthalmic lesions

Paul W. Miles, M.D.
Saint Louis, Missouri

Flicker fusion fields may be taken by determining for various areas the critical rate at which a flickering light of decreasing frequency is first perceived to flicker. Previous investigators[1] have agreed that flicker fusion fields are sensitive and "typical" in comparison to standard methods of taking fields. Last year's work showing the superiority of flicker fusion fields in the detection of early glaucoma[2] has been confirmed on subsequent cases.

Method

Flicker fusion fields may be taken at one meter on a gray tangent screen, or from behind a wire skeleton perimeter. The background should reflect about three foot-candles, and should be free from distracting details. The test is done in ordinary room illumination, and the patient is adapted to the same.

Repeatability is one to two percent over most of such a field, but begins to deteriorate beyond 30 degrees so that for peripheral fields flicker fusion frequency may be of less advantage.

The two eyes are tested separately with care that the occluder does not decrease the light intensity enough to affect pupil size or state of adaptation. The patient's glasses are removed, and spectacles with one white opaque lens are used for occlusion.

The Strobotron bulb used as a target is covered with thin white typing paper and has a cross section of about 3 by 5 cm. The bulb is mounted on a 24-inch wand connected by cable to the Strobotac† which lights the bulb for an exact 40 microseconds at any rate of flicker between 10 and 60 flashes per second.

The flash rate is reduced fairly rapidly to avoid fatigue, and to give the patient a definite sensation. The rate is read from a

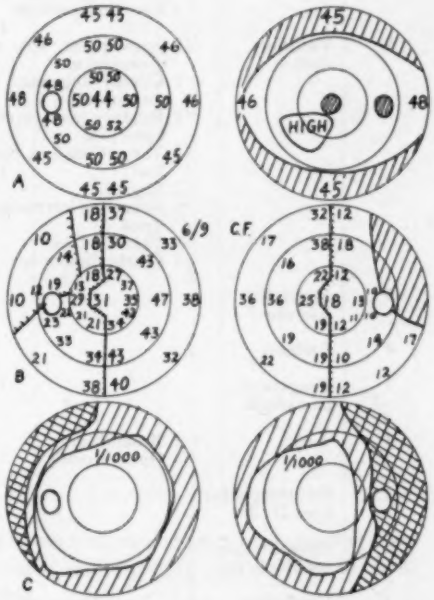

Fig. 1 (Miles). (A) The normal flicker field. The numbers refer to flashes per second at flicker fusion. Notice that the central three degrees is low and that the highest rate is inferior and nasal.

(B) Flicker fields of D. M., aged 50 years, who had chromophobe adenoma of the pituitary. The hatched area indicates perception of light but not flicker at 10 per second.

(C) Standard fields taken with 1/1,000 and 3/1,000 white at the same time. The defect is typical but not as complete as that shown by flicker field.

* From the Department of Ophthalmology and the Oscar Johnson Institute of the Washington University School of Medicine.

† The Strobotac is an instrument which has been in production for industrial use for 15 years. The price is reasonable. It is remarkably exact, and is as rugged and dependable as a modern radio. Information concerning the product may be obtained from General Radio, Cambridge, Massachusetts.

TABLE 1
PART A

SUMMARY OF DATA ON 47 PATIENTS COMPARES FLICKER FUSION FIELDS TO STANDARD FIELDS* (3/300 and 1/1,000 WHITE) AND TO OTHER CLINICAL FINDINGS

Cases	Disease	Type and No.	Standard Fields Localized			Flicker Fields Localized		
			None	Slight	Well	Poor	Well	Very Well
9	Chiasmal tumors	6 Pituitary adenoma	1	3	2		2	4
		2 Pituitary tumor	2			1	1	
		1 Nasopharyngeal	1					1
5	Parietal lesions	1 Meningioma, left	1					1
		2 Subdural hematoma	2				1	1
		1 Precentral gliosis	1				1	
		1 Encephalomalacia	1					1
9	Vascular disease	1 Angiospasm, ant. rt. choroidal art.	1					1
		1 Circoid angioma, rt. int. carotid	1					1
		1 Rupture mid. cerebr. aneurysm	1			1		
		1 Thrombosis mid. cerebral	1					1
		2 Migraine	1		1		1	1
		1 Aneurysm left cavern. sinus			1		1	
		1 Vascular lues	1				1	
		1 Cerebr. hemorrh.			1			1
9	Multiple sclerosis		7	2			2	7
4	Epilepsy		3		1		2	2
1	Congenital paraplegia		1				1	
4	Toxic	1 Bromidism		1				1
		3 Optic neuritis	2	1				3
2	Hydrocephalus (age 21, 34)			2			1	1
3	Optic atrophy (nonluetic)			3			3	
1	Cerebellar astrocytoma		1				1	
		Totals	29	12	6	2	18	27

* Perhaps standard fields could have been improved by expenditure of time and effort with reduced illumination, two-meter distance, and the use of colored targets.

dial and recorded on a clinical form sheet (fig. 1-A). The test is made in from 28 to 40 areas, depending on the patient's response. Central fields can be taken in most patients in about 10 minutes if an assistant records the numbers. Field contours of the usual kind can be made by inspection of the record compared to the normal (fig. 1-A).

CASE REPORTS

The following case studies (tables 1 and 2) were made in most instances by the neurologic departments of Washington University. The standard visual fields for comparison were taken by members of the resident staff of the ophthalmology department.

Of the 47 cases, flicker fields were defi-

TABLE 1
PART B
AIDS TO DIAGNOSIS CONFIRMING FIELDS

Confirmed by Neurologic Signs		Confirmed by Symptoms		Skull x-rays		Angiograms		Pneumoenceph.		E.E.G.		Surgery	
Yes	No	Yes	No	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
6		6		6								3	
1	1	1	1	2							1		
1		1		1								1	
1		1			1					1		1	
2		2			2			1	1			1	
1		1						1		1		1	
1		1								1			
1		1			1		1		1	1			
1		1		1		1			1	1		1	
1		1			1						1	1	
1		1		1					1	1			
2		2			2					2			
1		1			1		1		1	1			
1		1											
1		1											
7	2	9			4					1	2		
		4						1		2			
1		1			1				1		1		
1		1			1					1			
3		3			1						1		
2		2			2			1	1		1	1	1
3		3			2								
1		1										1	

nitely superior to standard fields in 28, slightly superior in 11. In 23 cases, flicker fields showed changes of localizing value where standard fields showed nothing. In no case was the flicker field inferior.

In some of the cases, for instance bromidism, no definite field change is to be expected. The flicker field was considered superior because of deeper patchy defects.

Figure 1-B and C shows how well flicker fields conform to standard central fields. Although the whole field in Figure 1-B is depressed compared to the rate numbers in Figure 1-A, the depression is greater in both temporal fields, and the drop in flicker rate is unquestionable in the paired readings across the vertical meridian. This patient was treated with surgery and X rays in June, 1948.

Figure 2-A, B, and C represents consecutive flicker fields in patient C. B., aged 24 years, with pituitary adenoma. The preoperative flicker field (fig. 2-A) showed definite bitemporal loss while standard fields showed merely concentric constriction. Postoperative fields (fig. 2-B and C) showed the effect of trauma to the right optic nerve and macular fibers. Standard visual fields showed a similar picture to a lesser degree.

Figure 3 illustrates the superiority of flicker fields in the case of B. A., aged 45 years, who had a circoid angioma of the in-

ternal carotid artery near the right anterior clinoid process. He had attacks of sudden headache, neck stiffness, vomiting, weakness of the left arm, blurring, diplopia, and memory changes. He had vertical nystagmus on looking right, rotary nystagmus on looking left or upward, left facial weakness, and a positive left Babinski reflex. Preoperative flicker fields (fig. 3-A) showed complete left homonymous hemianopia; while central 1/1,000 white showed nothing; and peripheral fields (fig. 3-B) showed slight constriction. Postoperative flicker fields (fig. 3-C) showed greater hemaniopia, but standard fields remained normal.

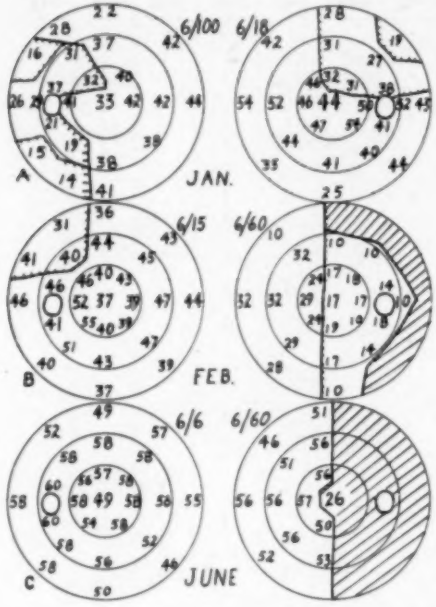

Fig. 2 (Miles). (A) Preoperative flicker fields of C. B., aged 24 years, show bitemporal loss. Standard fields (not illustrated) failed to suggest pituitary disease. Notice metric visual acuity.

(B) After removal of the tumor, the defect of the right eye increased, the left recovered. Standard fields showed slightly less change.

(C) Five months later. Standard fields also showed complete right hemianopia.

Figure 4-A illustrates the case of W. B., aged 58 years, who had thrombosis of the left middle cerebral artery, with pain, weakness, numbness and tingling of the right arm and hand, personality changes, and aphasia. He had paresis of the right face, protrusion of tongue to left, no papilledema. X-ray films showed calcification of the internal carotid arteries. Although standard fields were normal, flicker fields showed nearly complete right homonymous hemaniopia.

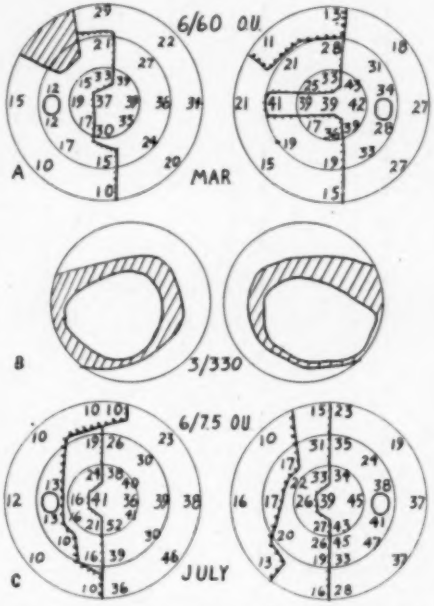

Fig. 3 (Miles). (A) Preoperative flicker field of B. A., aged 45 years, showing left homonymous hemianopia due to circoid angioma of the right internal carotid artery.

(B) Standard central fields (not illustrated) were normal. Peripheral fields were merely constricted.

(C) Postoperatively, visual acuity improved; flicker fields showed hemianopia while standard fields showed nothing.

Nine cases of multiple sclerosis were studied with comparison of standard and flicker fields. V. R., aged 24 years, was tested in June and November, 1948, and December, 1949. M. P., aged 28 years, and D. M., aged 29 years, were also tested repeatedly. All three patients showed that flicker fields follow the remittent optic neuritis, but

with more time lag than with standard fields. In the acute phase, both flicker fields and standard fields are depressed. After two months, however, the standard fields may become normal, while flicker fields remain depressed for six months, then begin to improve. None returned to normal.

Figure 4-B and C illustrates the ever changing flicker field of multiple sclerosis.

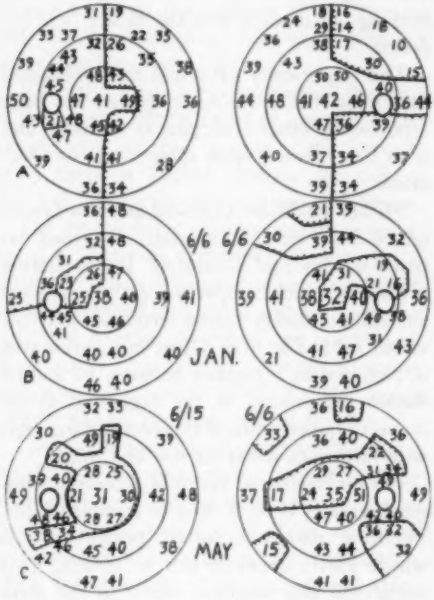

Fig. 4 (Miles). (A) Flicker fields of W. B., aged 58 years, who had a typical thrombosis of the left middle cerebral artery. Standard fields at the same time were normal, peripheral and central.

(B) Fields in D. M., aged 29 years, with multiple sclerosis of five years' duration. Standard central fields were normal.

(C) Fields four months later were entirely different, with acute optic neuritis, left.

Flicker fields always showed irregular peripheral defects as well as the central or centrocecal scotoma found in standard fields. Of the total 18 cases tested, all showed either a central, a centrocecal, or a blindspot-enlargement defect; 15 showed patchy peripheral defects; six showed sector defects; three showed uniform peripheral loss; and three showed a tendency to hemianopia.

Figure 5-A illustrates the central scotoma found in the three cases of toxic optic neuritis. Theoretically, a small scotoma might be missed by the use of such a large target as the flicker bulb. Such a failure has not yet

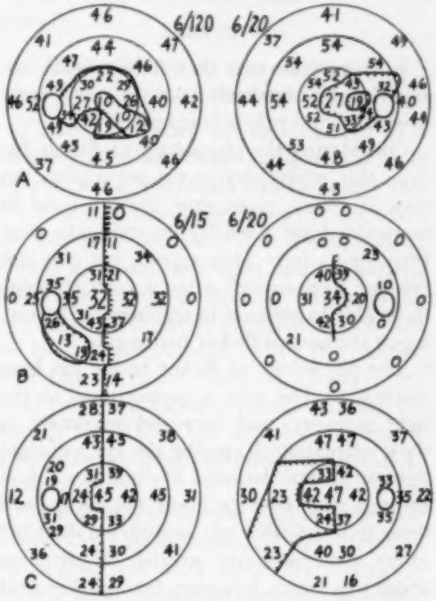

Fig. 5 (Miles). (A) By way of contrast, M. B., aged 35 years, had an acute toxic neuritis. Flicker fields show several gradations of density, while standard fields showed nothing, right, and a 10-degree central scotoma, 2/1,000 white, left.

(B) Fields in L. S., aged 43 years, migraine, right Bell's palsy with deafness, neuritis, right, nerves II, V, and VII. She had spells of left headache, choking, blurring, and coma. Standard fields showed merely concentric constriction.

(C) Fields in W. O., aged 38 years, who had injury and surgery to right skull five years ago, weakness of the left face and hand. Standard fields were entirely normal.

been found, except in amblyopia ex anopsia where central flicker in high.[3]

In the cases of unilateral brain disease studied where flicker fields showed a hemianopia, all corresponded to the diseased side. It was particularly interesting to find flicker field changes in vascular diseases of the brain, even in a proven vasospasm. Also, in the traumatic head injuries where visual

fields are not usually helpful, flicker fields showed lateralization.

The fields in patients classified as epilepsy in Table 1 were recorded as superior by the flicker method because the general and patchy field depression was more marked.

Discussion

It is very certain that flicker fields are superior to standard fields in very early cases of neuro-ophthalmic lesions.

Considering the physiology of flicker fusion, this superiority is not surprising. An area of retina, given time, may respond to minimum light intensity, to minimum contrast, or to form (test types), but may not recover soon enough after a flash stimulus to be able to respond to another test following at the normal flicker fusion rate.

The physiology of flicker fusion has been discussed.[1] The rate is proportional to the light intensity, and decreases markedly in dark adaptation. Exposing the eye to bright light or to total darkness five minutes before the test may raise or lower the entire field three to five flashes per second, but does not affect field contours greatly. It requires about two hours, however, for a flicker field to return to normal after the pupil is made artificially small in uniform light.[4]

Normal menstruation has an effect on flicker fields. Flicker fields were taken on 18 young women on the 2nd, 10th, and 27th day of each menstrual period for two complete cycles. Most of them showed general elevation of the entire field just before menstruation. The part of the field above and below the blindspot varied less, with a tendency to be lowered during menstruation. This variation was not found when the fields were taken on 10 young men at the same time intervals.

Summary and Conclusions

Flicker fields correspond in contour to those taken with standard technique, but show more sensitivity, particularly in early cases where fields are most valuable. Of the 47 cases described in this paper, flicker fields were considerably superior to standard fields in 28, and slightly superior in 11. In 23 of the cases, flicker fields showed changes of localizing value where standard fields showed nothing. In no case was the flicker field inferior.

This superiority of visual fields obtained by testing flicker fusion frequency has been reported by other clinicians in the past, and is to be expected upon theoretical considerations.

Flicker fields are practical and can be obtained from sick and mentally disturbed patients quickly and accurately. Interpretation is made by quick comparison with the normal variation of flicker fusion frequency over the visual field. The field defect in a given area is recorded as a number between 10 and 60 flashes per second, so the degree of visual loss is obtained without time-consuming tests with targets of different size and color.

Flicker fields in multiple sclerosis show much greater defects than do standard fields. There is always a patchy peripheral loss which varies from month to month. This peripheral loss was not found in the three toxic neuritis cases studied.

Flicker field changes of lateralizing value were found in unilateral brain conditions like trauma, arterial spasm, aneurysm or occlusion, and thrombosis.

640 South Kingshighway (10).

I gratefully acknowledge the help of members of the house staff and visiting physicians who gathered the clinical data reported here.

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FURTHER CONSIDERATIONS OF FIXATION DISPARITY AND THE BINOCULAR FUSIONAL PROCESSES

KENNETH N. OGLE,* PH.D., AND AVERY DEH. PRANGEN,† M.D.
Rochester, Minnesota

The fusion compulsive reflex through particular synergies to the extraocular muscles strives to direct the pointing of the eyes so that like images fall as near as possible on corresponding retinal points.

Recently[1] it has been emphasized that this pointing may not be exact if heterophorias‡ are present, but that, in spite of this inexactness, there is fusion because the images will still fall within Panum's areas of fusion.

The deviation between the images is designated a "fixation disparity." It occurs because the eyes are actually overconverged or underconverged by a small amount from the object of fixation, owing to the compulsion of an active heterophoria. Though fusion is maintained the images of the fixation point actually fall on disparate retinal points.

The magnitude of this disparity, the angular error in the convergence of the eyes, is necessarily small, being limited by the size of Panum's areas, and accordingly is measured in minutes of arc. Its magnitude depends on many factors[1], but remains relatively constant for the same individual when measured under similar test conditions.

The accumulation of many more data§ on this phenomenon since the preliminary publication permits us to interpret the results somewhat more broadly and to revise several of the earlier points of view.

BRIEF RÉSUMÉ OF THE METHOD OF MEASUREMENT

Fixation disparity can be measured by a simple vernierlike visual configuration, with which (for a horizontal measurement) one eye sees only the upper line while the other eye sees only the lower line. These vernier lines are viewed on a large detailed pattern which stimulates fusion of the images in the two eyes. With the appropriate instrument the horizontal separation of the two vernier lines can be varied until the observer reports that they appear aligned, one directly beneath the other. The actual displacement is the fixation disparity under those conditions.

For a distant vision test (2.5 meters), the subject views through polaroid plates Snellen charts projected on a screen by a lantern. Upon a small blanked-out area at the center of the charts the two narrow vernier lines are also projected by a second lantern. Polaroid film can be arranged before these lines in such a way that one eye sees only the upper, the other eye only the lower line. The upper line is stationary; the lower can be displaced horizontally by a suitable screw in the lantern by the experimenter. The amount of displacement is indicated on an appropriate dial. By means of a shutter the lower line can be flashed or exposed for any period of time. Rotary (Risley) prisms or ophthalmic lenses can be conveniently placed before the eyes of the subject.

At the near visual distance (29 cm.) a photographic transparency which has similar details to those described for distant vision replaces the screen and projection lanterns. For a more detailed description of the instruments the reader is referred to the earlier paper[1].

* From the Section on Biophysics and Biophysical Research, Mayo Foundation and Mayo Clinic.
† From the Section on Ophthalmology, Mayo Clinic.

‡ The term "heterophoria" is used here in its generic sense to mean a *tendency*, and in particular a tendency for the eyes to deviate from correct pointing.

§ The results reported in this paper are based on the studies on about 150 subjects, the majority of whom were Mayo Clinic patients.

In the test the experimenter instructs the subject to look at the upper vernier line, and then the lower is flashed for a fraction of a second. The subject is asked to report whether the momentarily seen line appeared to the right of, to the left of, or centered with the upper line. Between exposures the lower line is adjusted to a new position. The limits of the range within which the lower line can

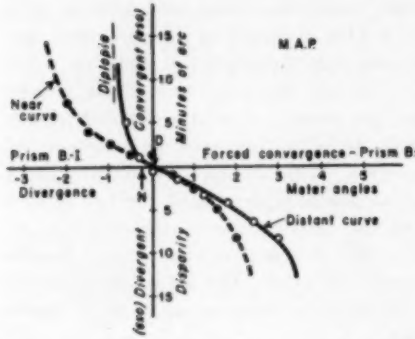

Fig. 1 (Ogle and Prangen). Typical fixation disparity versus forced convergence-divergence.

be displaced and the subject reports that the two lines appear one directly below the other can be obtained.

The distance between the stationary line and the midposition of the range of the movement of the lower line is the fixation disparity, and this is expressed as the angle (in minutes of arc) subtended by this distance to the subject. Subjects with good visual acuity in both eyes and with a low degree of muscle imbalance can usually make the discrimination within one minute of arc.

It will be clear that, in this test, fusion is prevented at the center of the fovea, and that the fixation disparity measured is the disparity between the images which are fused extrafoveally. The phenomenon, however, is the same irrespective of this fact. The actual magnitude of the disparity might be less if the fused images included more of the foveal regions.[1]

RESULTS

The change in the fixation disparity when the eyes are forced to converge or diverge with prisms, and again when the stimulus to accommodation is changed by spherical ophthalmic lenses before the eyes, especially at a near visual distance, is of special interest, for the data of each subject yield a graph that is characteristic of his particular binocular behavior in the test.

In the prism vergence tests, Risley prisms are used. The prism power is placed alternately base-out and base-in; the base-out strength of the prism power is increased in 4^{Δ} steps and the base-in strength in 2^{Δ} steps, except at near vision and when a high exophoria is present, when also 4^{Δ} steps are used. The alternation of base-out and base-in tends to prevent the cumulative and residual effects.

A typically normal set of data when plotted gives the sigmoid type of curve shown in Figure 1. The abscissas are the meter angles of forced convergence (prism base-out) or forced divergence (prism base-in) (one meter angle is equal to 6.4 prism diopters for an observer whose interocular distance is 64 mm.); the forced convergence is taken to the right. The ordinates are the measured fixation disparity in minutes of arc; convergent (esophoria) upward, divergent (exophoria) downward.

The curve shows that when the eyes are forced to *converge*, this convergence lags to the extent indicated by the increasing fixation disparity in the *divergent* direction; when forced to diverge, this divergence lags to the extent indicated by the increasing fixation disparity in the convergent direction. As the end-points of prism vergences are approached, the fixation disparity very rapidly increases and finally diplopia occurs.*[2]

* Hofmann and Bielschowsky have already reported that in fusional amplitude tests in the stereoscope, and by the use of suitable control lines, the visual axes of the eyes may be seen to lag behind

These graphs are more instructive and less confusing when the data are plotted in terms of the absolute angle of convergence, as shown in Figure 2. The abscissas then give the actual convergence of the eyes in meter angles, a scale which indicates as well the equivalent diopter distance to the point of convergence. The origin of the graph, zero meter angles, represents the primary position of the eyes when their visual axes are parallel.

Since the actual test for distant vision was conducted at 2.5 meters, the convergence would be 0.4 meter angle; for the near test, for which the distance was 29 cm., the convergence would be 3.4 meter angles.

The use of prisms base-in or base-out forces the convergence of the eyes from these positions. Thus the actual curves in this figure are identical with those of Figure 1, except that they are displaced to the right corresponding to the test distances.

The lateral heterophorias of the subject measured with eyes disassociated are indicated on these graphs by short arrows, and

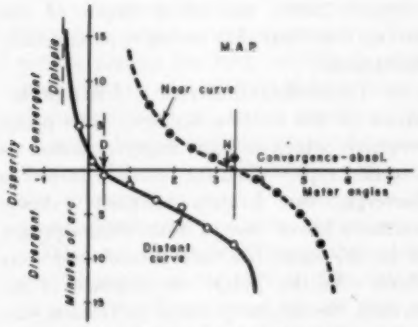

Fig. 2 (Ogle and Prangen). The data of Figure 1 plotted in terms of the absolute angle of convergence.

these are identified by the letters D and N, for distant and near vision. The heterophoria with fusion would be given by the place where the curve intersects the abscissa; the fixation disparity is zero for this place.

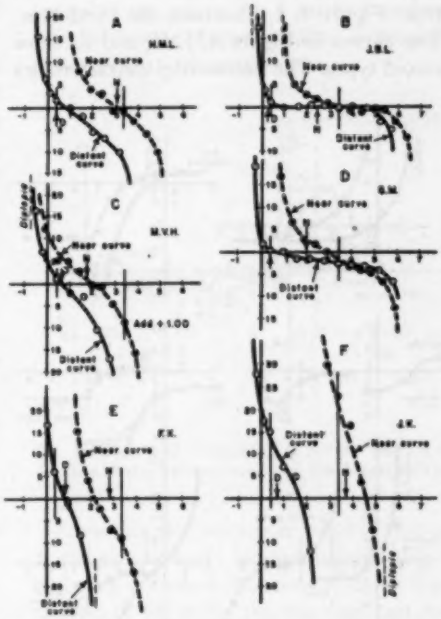

Fig. 3 (Ogle and Prangen). Typical examples of fixation disparity-prism vergence curves.

Types of curves

Two types of curves were distinguished originally,[1] probably because at that time most of the data had been obtained on subjects with normal or near-normal eyes. These two types of curves, of which those in Figures 1 and 2 are representative, probably belong to one general type, as will be shown later. Two new types are distinguishable as a result of the more recent data, though these occur much less frequently than the original type.

Figures 3 and 4 show 12 curves which have been selected as examples to illustrate certain special or typical features. These data are all plotted on the absolute convergence scale as in Figure 2.

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the target displacement. This lag seemed to increase the nearer the limits of the fusional amplitudes were approached.

The curves, A through F, Figure 3, are examples of the typical and most frequently found curve. Those designated G and H, Figure 4, represent examples of the second type. Figure 4, I, illustrates the third type. The curves in Figure 4, J, K, and L, show mixed types. The noteworthy characteristics

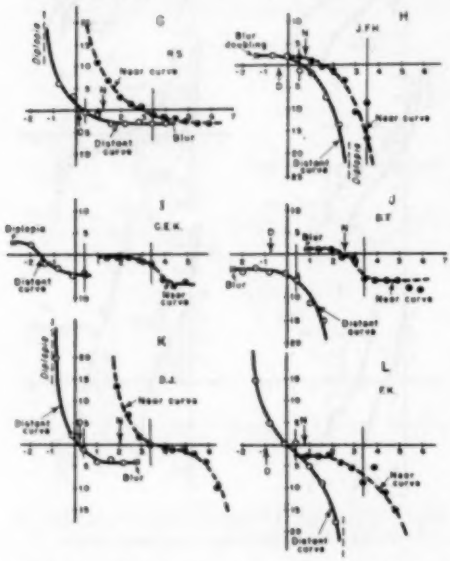

Fig. 4 (Ogle and Prangen). Typical examples of fixation disparity-prism vergence curves.

of each of these examples are as follows:

A. This is a fairly normal pair of curves that show only a small esophoria at distant vision and a small exophoria at near. The curves drawn through the data points are identical and symmetrical for both distant and near. Ideally the curves should pass exactly through the 0.4 and 3.4 meter angle positions on the abscissa.

B. This set of data illustrates a high degree of fusion and of muscle coördination. The fixation disparity remains nearly zero over a wide range of prism vergences, for both distant and near vision, in spite of the six prism diopters of exophoria at near.

C. These data are for a subject with a convergence difficulty at near vision. The (exo) fixation disparity is very large at near, and the subject's hold on fusion is far too near the point of diplopia. The prism base-in end-points for both distant and near vision appear to be the same, points which are probably determined only by neuro-anatomic or physiologic limitations.

D. The curves for this subject illustrate a marked difference in the slopes for distant and near vision. The end-points for convergence (prisms base-out) appear to be the same for both distant and near vision.

E. These curves illustrate the data of a subject with a marked esophoria for distant and a marked exophoria for near vision. The magnitude of the phoria at near vision, measured with disassociated eyes, does not really indicate the degree of imbalance with fusion.

F. This subject had undergone operation to reduce an intermittent convergent strabismus. A residual esophoria remained, which when the eyes were associated caused a large (eso) fixation disparity. With the low prism vergence limits, and steep slopes of the curves, it is clear that fusion is precariously maintained.

G. These data illustrate a different behavior of the fixation disparity with prism vergence, which is accordingly classified as a second type. When the eyes are forced to converge, the fixation disparity slowly reaches a lower limit, a limit which appears to be the same for both distant and near vision. As the prism convergence is increased, the disparity tends to remain constant until finally blurring and confusion set in; then perhaps a diplopia unobtrusively follows. The appearance of the diplopia is gradual and not dramatic as for the prism divergence limit, or for both limits in the normal sigmoid curves.

H. These data of another subject illustrate the same type of curve as in G, except that the petering out of the curves occurs with the prisms base-in; that is, with forced divergence.

I. A third and even more infrequently found type is illustrated here. This type is usually found with subjects having some fusion difficulty. Subjects in this group respond only to a limited extent to either forced convergence or divergence.

J. These data illustrate a mixed second and third type in their different behavior at distant and near vision. Note that at distant vision the curve never crosses the abscissa, that there is no prism vergence for which the disparity can be made zero or convergent.

K. These data also illustrate mixed types, for distant and near vision. The normal curve is at near vision, and the fixation disparity is essentially normal at distant vision, but the curve fails to become more convergent than four minutes of arc with increased forced convergence (prisms base-out).

L. These data illustrate also a mixed first and second type. For the distant vision test a normal curve is found, while for the near vision test, where the patient has a convergence difficulty, the disparity never becomes zero or goes in the convergent direction.

The fixation disparity curve obtained in the prism vergence test represents a characteristic pattern for each individual subject, and within physiologic variations it is usually repeatable. Such a curve, therefore, indicates the motor imbalance and the motor-fusion behavior for each subject as his eyes are subjected to forced convergence and forced divergence caused by the prisms.

What are the explanations of these different behaviors on the part of different subjects? From these curves can we gain any clearer concepts about the nature of the binocular fusional processes?

Relationship of fixation disparity to lateral heterophoria

While the direction of the measured fixation disparity usually appears to be the same as that of the lateral heterophoria, it was evident that the correlation between the quantities would not allow us to predict one on the basis of the other.

Figure 5 is a scatter plot of the fixation disparity and the heterophoria, in which both the distant and near measurements have been plotted. Inspection shows a broad scattering of the points but a marked tendency for the fixation disparity to be in the same direction as the heterophoria.

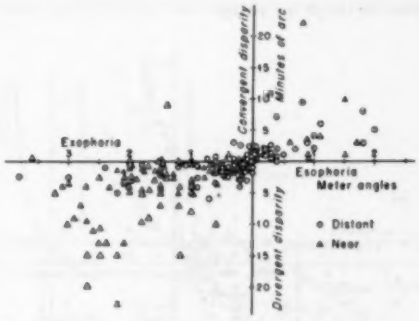

Fig. 5 (Ogle and Prangen). A scatter plot of the fixation disparity measured and the heterophoria.

From this plot, one meter angle (6.5 prism diopters) of phoria is very roughly associated with a fixation disparity of about three minutes of arc under the described test conditions. However, an inspection of such curves as those shown in Figures 3 and 4 clearly indicates that the magnitude of the disparity will depend not only on the general slope of the fixation disparity curve but also on the position of the end-points of that curve relative to that convergent position of the eyes at which the test was made.

We cannot therefore predict the magnitude of the fixation disparity on the basis of the magnitude of the phoria. However, a large fixation disparity indicates generally a marked heterophoria.

Interpretation of Figure 5 must take into account the inaccuracy and variability of the phoria measurement. The phoria measurements were made by the Maddox-rod test, in which the light from the rod was exposed only momentarily to the subject. This technique tended to reduce any voluntary convergence on the part of the subject to align

the Maddox light streak with the light source.

For the near visual distance, in addition to the small muscle light, there were other details seen by one eye to stimulate the accommodation. The possibility of a lagging accommodation at near when only one eye receives the stimulus to accommodation must also be kept in mind.

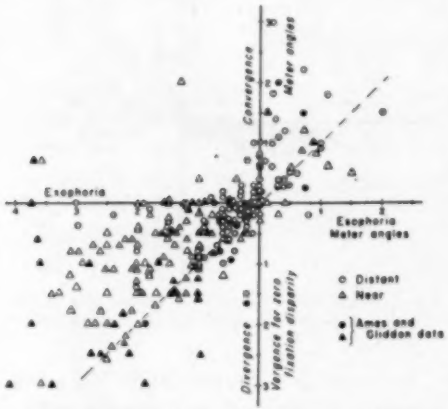

Fig. 6 (Ogle and Prangen). A scatter plot of the phoria and that corresponding prism vergence which makes the fixation disparity zero.

Verhoeff[3] has pointed out that the heterophoria, as usually measured, is a "presumptive heterophoria"; we presume that this measurement obtained with disassociated eyes is a measure of that tendency for the visual axes to deviate from the correct positions when *fusion exists*. While the fixation disparity must be a measure of the heterophoria with fusion, its magnitude alone can be used only approximately as such a measure. Clearly more information than the magnitude alone is necessary in order to evaluate the significance of the fixation disparity measured.

An approach to answer the question whether the phoria measured in disassociated vision can be presumed to be the phoria that exists when fusion is present, is to correlate the disassociated phoria with that prism vergence where the fixation disparity curve crosses the abscissa. At this point the fixation disparity is zero, and this fact indicates the prism vergence at which no muscle imbalance exists.

Figure 6 shows a scatter plot of these data, for distant and near vision. Also included are the data published by Ames and Gliddon,[4] which were simply obtained by turning the arms of the haploscope until the subject reported no fixation disparity. A number of points corresponding to phorias (and tropias) greater than four meter angles are omitted for lack of space.

An inspection of Figure 6 shows that in many cases the phoria measurement does correspond approximately to the vergence where the fixation disparity is zero. In many others, however, a large difference exists. This difference is especially pronounced in the intermittent squint cases, as would be expected.

In general, the chart shows a tendency for the points to be displaced somewhat in the direction of exophoria. In fact, few are the cases where the phoria measured with disassociated eyes is greater than the corresponding prism vergence for a zero fixation disparity (the heterophoria with fusion).

Quite frequently in these fixation disparity tests, the phoria measurement lies near the limit of the base-in vergence and sometimes it is even found to lie entirely outside the range of prism vergences, within which fusion is maintained. This state of affairs is rarely found in ordinary prism-vergence tests except in subjects with intermittent exotropias.

In the usual tests the prism power is gradually increased with rotary prisms until the limit is reached; whereas, here the subject's eyes are held at each successive prism vergence for one or two minutes while the fixation disparity is being measured. The amplitudes here should be smaller generally than those obtained with continuous change in the prism power.

Of special interest is the case illustrated in Figure 7, that of a man, aged 26 years, with a high myopia (R.E., −3.5D. sph. ⌒ −2.5D. cyl. ax 60°; L.E., −8.5D. sph.

⊂ −2.25D. cyl. ax. 145°). The space-eikonometer test gave: ×90: L 0.5%±0.5, ×180: L 0.5%±0.5; and ϑ: +0.4°±0.3.

Though a small cyclotorsion may have masked a possible meridional aniseikonia at oblique axes because of the astigmatic errors, the test shows that the ocular images are essentially equal and normal stereopsis is present.

The curve at distant vision is essentially normal and the distant phoria (2^{Δ} exophoria) agrees with the crossing point of the curve. At near vision, however, where the manifest phoria, uncorrected for the prismatic effect of the subject's glasses, varied from a large exophoria at the beginning of the test to a small esophoria at the end, the curve is greatly displaced in the direction of a marked esophoria. A large fixation disparity exists with no prisms at near, and the point where the curve crosses the abscissa indicates an esophoria of about 16 prism diopters!

Probably in this myope the accommodative processes are poorly developed, and the excessive accommodative effort needed for clear retinal images induces the large esophoria. Full accommodation may not have been attained with disassociated eyes; hence the exophoria measurement.

The data for this curve are understandably more variable than those normally found. Nevertheless, one would not expect an esophoria to exist here. In the light of these results perhaps this fact could also be deduced from the usual prism vergence test, if carefully made.

These data show that the heterophoria measured with eyes disassociated often cannot be presumed to be a measure of the heterophoria that exists when fusion is maintained.

Processes involved in the fixation disparity-prism vergence curves

Fixation disparity is the manifest difference in the tonicity of the extraocular muscles resulting from the convergence and the divergence muscular synergies, together with the influence of mechanical and neurologic limitations of those muscles. The latent diplopia so expressed is held in check by the compulsion-to-fusion reflex. An expenditure of nervous energy is implied in maintaining an equilibrium between these processes. When the eyes are forced to converge or to diverge by prisms the tonicity difference is changed, and this in turn is reflected in a change in the fixation disparity.

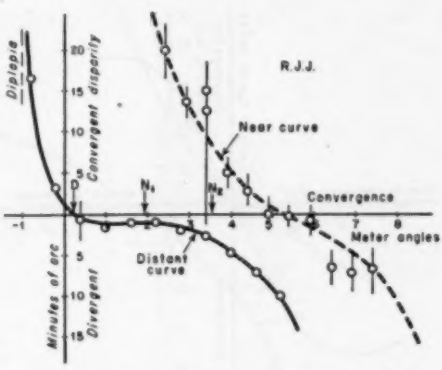

Fig. 7 (Ogle and Prangen). The curves of a high myope showing the marked condition of esophoria when fusion is maintained, though the initial exophoria measurement was found.

1. The fusion reflex. The primary activity of the fusion reflex is to prevent diplopia: to prevent the appearance of double images. However, for horizontal disparities there appears to be a voluntary as well as an involuntary aspect of this reflex.

In the ordinary use of the eyes when the binocular visual field contains many objects at different distances, and when therefore there are many different degrees of horizontal image disparity, there is a psychic factor to the fusion reflex which inhibits the compulsion to fusion of all disparate images except those to which attention is drawn.

Once attention is given to an object, the fusion reflex then takes command, and the fusion reflex acts as a true involuntary reflex.[5] In prism vergence tests the voluntary part of the fusion reflex is very small, except perhaps near the end-points when the

subject exerts an extra effort to maintain single vision.

The strength of the innervations to the convergence or divergence muscular synergies under the compulsion of the fusion reflex must be greatest when the disparity of the images in the two eyes is near the point of doubling. As soon as the disparity is such that the images fall within Panum's

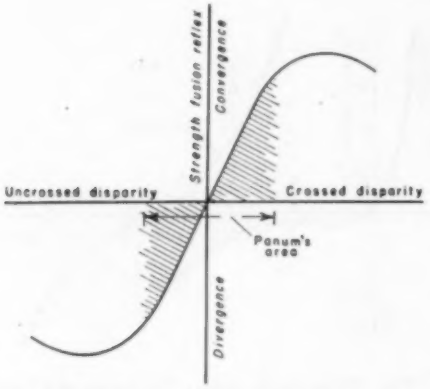

Fig. 8 (Ogle and Prangen). A schematized illustration of the probable relationship between the strength of the innervations from the fusion reflex and the disparity of the retinal images.

areas, diplopia no longer exists, and the primary goal of the fusion reflex is attained though the images may not yet fall on corresponding retinal points. The fusion compulsion from widely disparate images seen in double images is of course much reduced.

Now the existence of the phenomenon of fixation disparity and the shapes of the curves shown here must imply that once the images are within Panum's areas, the fusion reflex still strives to so direct the eyes that like images fall as near as possible on corresponding retinal points. But the strength of the innervation from the fusion reflex decreases as the disparity becomes less, that is, as the images come closer and closer to their falling on corresponding retinal points.

We might picture the general quantitative relationship between the strength of the involuntary fusion compulsion and the disparity of the images ideally as that shown in Figure 8.

When the images are precisely superimposed (zero disparity), the fusion compulsion is inoperative. But if we try to separate the images, this compulsion exerts itself and its strength increases sharply as the disparity is increased until a maximum is obtained, beyond which that compulsion gradually decreases.

A range of disparities in the central portion of the graph would correspond to Panum's areas of fusion—within which single binocular vision exists. Outside this region with its somewhat indefinite limits, images would normally be seen double.

The steepness of the central portion of the curve, on the one hand, and the positions of the maxima, on the other, would be measures of the relative strength of the fusion compulsion. These will differ between individuals, different parts of the retinas, and the amount of detail and brightness contrast in the retinal images.

It is clear that an existing heterophoria must be constantly compensated for by the compulsion to fusion reflex. That is to say, the compulsion to fusion will actively offset those mechanical and innervational factors influencing the convergence or divergence synergies that tend to cause a deviation of the eyes from the correct pointing.

To maintain an equilibrium only that degree of fusion compulsion necessary to equalize the heterophoria will be exerted. However, the pointing of the eyes can then actually deviate in the direction of the heterophoria by the amount of disparity corresponding to this degree of the fusion compulsion being exerted, as suggested in Figure 8.

When the heterophoria is greater, a greater degree of compulsion is needed, but accompanying this will be a greater disparity. If the heterophoria exceeds the maximal possible compulsion to fusion, diplopia occurs at once.

It should be clear that the course of the fixation disparity data, as obtained in the test set-up described here, results from an integrated response of the compulsion to fusion that involves the extrafoveal regions of both eyes. Certainly if the fixation disparity is large, exceeding about 10 minutes of arc, then the fusion near the macula must be imperfect if not nonexistent; the fusion is then maintained by more peripheral retinal parts.

2. The accommodation-convergence reflex. In the prism vergence tests the accommodation-convergence association reflex and the reflex to the accommodative mechanism for the maintenance of clear retinal images play important roles.

If one is forced to accommodate when negative lenses are placed before the eyes, an impulse to converge occurs almost simultaneously. The actual change in convergence in the absence of fusion (called in the literature the "accommodative-convergence") indicates on the one hand the degree of association between the accommodative and the convergence mechanisms and, on the other, the ease and extent to which the accommodation demanded is obtained.

The evidence that this relationship also holds when fusion is maintained is shown by the measurement of the fixation disparity when a sequence of spherical ophthalmic lenses are placed before the eyes at the reading distance. Figure 9 illustrates the data obtained on two subjects.

Now going a step farther, we can find the equivalent meter angles of forced convergence corresponding to any one of those fixation disparity data points by referring to the sigmoid fixation disparity-prism vergence curves (as, for example, Figure 7 for the subject R. J. J.).

Making this translation of data for the two subjects here, we then plot the resulting data to show the relationship between the accommodative change caused by the lenses and the equivalent change in forced convergence (or divergence).

Figure 10 illustrates these data. The linear relationship between these quantities is clear.* Only when the images begin to blur for subject M. C. does this linearity change, and obviously the presence of blur shows that the accommodation has not responded to the lens power. In these curves we are working within the shaded area of Figure 8.

Now the change in the convergence inner-

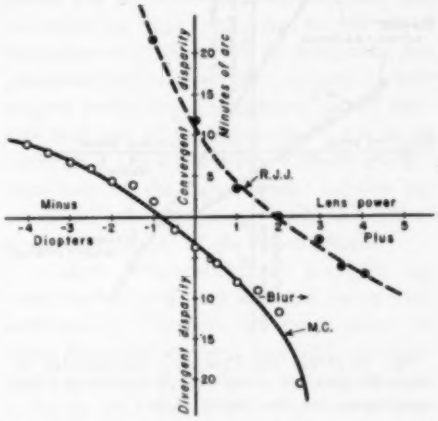

Fig. 9 (Ogle and Prangen). Data illustrating the influence of spherical lenses on the fixation disparity for two subjects; an esophore (R. J. J.) and an exophore (M. C.). Observation distance was 29 cm.

vations caused by spherical lenses when fusion exists, parallels the change in accommodative-convergence with the same lenses as measured by the Maddox rod with the eyes disassociated. In Figure 11 are illustrated these data for one subject.

In this case the two sets of data appear identical, because the original heterophoria agreed with the prism vergence at which the fixation disparity was zero. In other cases in which the heterophoria did not agree the two sets of data run a parallel but linear course.

These data are evidence that the change in convergence associated with a change in

* The small correction for the prismatic effect of the lenses at the near observation distance has been neglected. Their effect would not change this linear relationship.

the accommodation manifests itself fully when fusion is maintained.

It is reasonable to assume that the particular degree of accommodation and that of the associated convergence can be the result of primary innervations sent either to the accommodative mechanism in the interest of clear vision inhibits that innervation to accommodate arising from the accommodation-convergence association.

In turn, this inhibiting innervation, through the accommodative-convergence association, provides the innervation for a divergence (prisms base-out) or a convergence (prisms base-in). This assumes that the accommodation-inhibiting innervation in this circumstance is equivalent to the normal accommodation-relaxing innervation associated with relative divergence or convergence relaxation.

Thus in the prism vergence test we have a complex interaction of two opposing reflexes which resists the forced vergence. As the forced convergence (or divergence) is increased an end-point will occur when the reflex for clear vision can no longer offset the innervation to change the accommodation arising from the accommodation-convergence reflex. It is difficult to account for the resistance of the convergence or divergence muscular synergies to the forced convergence or divergence in the prism vergence test ex-

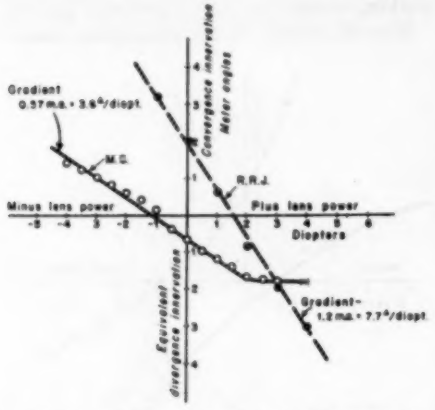

Fig. 10 (Ogle and Prangen). Relationship between the spherical lenses and the equivalent forced convergence for the data of Figure 9.

accommodation or to the convergence synergy. The innervation for a change in convergence is proportional to the innervation necessary to change the accommodation, and vice versa.

The linear relationship between the two over the range of accommodation employed (over seven diopters for this subject) found here suggests that the effort to accommodate from six to seven diopters is the same as that from one to two diopters. The degree of this effort will of course vary greatly between individuals, as the data in Figure 10 show very well.

It may be assumed that when the eyes are forced to converge by means of prisms (or a haploscope) with a constant observation distance (a constant stimulus to accommodation), an equivalent impulse for a change in accommodation occurs. This change is not manifest, however, because the reflex to the

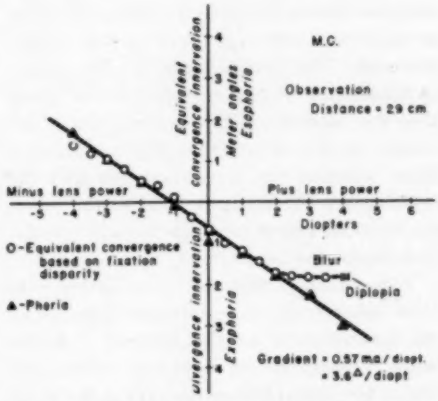

Fig. 11 (Ogle and Prangen). Data showing that the change in convergence associated with the change in accommodation caused by spherical lenses follows the same linear course with disassociated eyes or when fusion is maintained.

cept on the basis of these opposing reflexes.*

It is not unreasonable to assume that the relationship between these reflexes is also *linear* at least until the images begin to blur, when the reflex for clear vision can no longer offset the influence of the accommodation-convergence association. We can infer then that the linear relationship between these functions exists in the sigmoid curves. These curves, in turn, would then illustrate to a large extent the shape and magnitude of the compulsion to fusion-disparity curve (fig. 8).

3. The symmetry of the curves. One of the striking facts of the sigmoid curves is their symmetry in the converging to diverging directions. Especially is this true of the curves obtained at near vision. In the graphs given here the curve through the points in nearly every case is the symmetrical curve. In several instances the center of symmetry is indicated.

If there is no muscular imbalance at near vision, the position of the center of symmetry should coincide with the origin (fig. 1). This symmetry suggests that the mechanisms of the accommodation-convergence reflex and the accommodation reflex to preserve clear vision as they function in these prism experiments are the same in the convergent as in the divergent directions; the same whether the mechanisms are stimulated to accommodate or to relax. There would be no reason for assuming that the fusion compulsion reflex would be unsymmetrical with regard to crossed and uncrossed disparities.

Heterophorias are sometimes divided into three categories: the basic (essential, static) heterophorias, which are those due to mechanical or structural factors that impede the eye movements; the functional (kinetic, symptomatic) heterophorias, which are due to anomalies in the accommodation-convergence synergy (including refractive errors); and finally neurogenic[6] heterophorias.

Upon the basis that the symmetry of the curves for near vision expresses the symmetrical relationship of the association between the accommodation-convergence and the reflex for clear vision, then the horizontal displacement of the curve, the horizontal displacement of its center of symmetry with respect to the test convergence, should indicate that part of the heterophoria due to an anomaly in that association. The vertical displacement of the curve would indicate the combined influence of the basic and neurogenic components of the heterophoria.

In about 30 percent of the cases the sigmoid curves for distant and near vision were substantially identical. In these cases we could assume that the functional synergies between the accommodative-convergence association and the reflex to preserve clear vision were the same for both distant and near vision. However, in all these cases the center of symmetry of the distant curve (for example, fig. 3-A) is displaced in the direction of esophoria. On the average this displacement is about 1.2 meter-angles!

The majority of the other sigmoid curves which were not the same at distant and near showed a larger prism vergence range at near vision than at distant. If the same association is operative at distant as at near vision, we shall have to assume that the end-point in the base-in forced divergence is determined by the neuro-anatomic limitation of the disjunctive eye movements. Hence the otherwise normal curve is cut off more abruptly on the divergence than on the convergence side.

There are cases, of course, that show a marked difference in the pattern of behavior between distant and near vision. In these the exact function of the various mechanisms involved must also be a function of the abso-

* It is possible that another unknown factor is also involved, for in absolute presbyopia a range of prism vergences not determined wholly by neuro-anatomic limitations is also found. We could account for this range otherwise only on the assumption that the reflex for clear vision arises from neural associative connections in the higher centers, and does not result directly from the blurredness of the retinal images.

lute convergence (and accommodation) itself.

Occasionally curves are found in which part of the curve is flat over a range of forced prism vergences (as, for example, the distant curve in fig. 7). The constant fixation disparity in this region might represent the influence of the basic heterophoria, in a

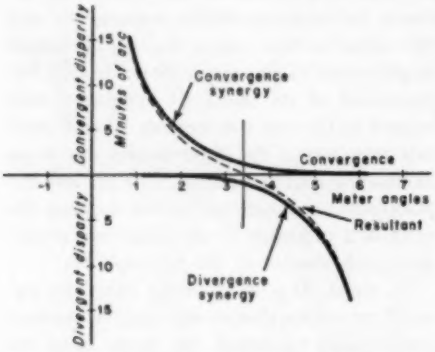

Fig. 12 (Ogle and Prangen). A fixation disparity-prism vergence sigmoid curve can be described as the sum of two separate component curves.

region where the accommodation-convergence association is loosely held, or the fusion reflex is unusually strong.

4. The two components of the curves. An analytic study suggests that the sigmoid fixation disparity curve can be described as the composite of two separate curves, as schematically illustrated in Figure 12. In fact the majority of the curves can be satisfactorily described by $y - C = A\,e^{ax} + B\,e^{-bx}$ where x is the degree of forced convergence (or divergence; for which x will be negative) and y is the fixation disparity. A, B, C, a and b are constants. A curve which is symmetrical about the origin of the graph has $A = B$, $a = b$, $C = O$. C of course is the constant fixation disparity throughout the data and describes the vertical displacement of the curve. By adjusting the other constants, most of the sigmoid curves can be described by such component curves, irrespective of their shapes.

These component curves suggest the activity of the two opposing muscular synergies; the upper one describes the action of the convergence synergy, the lower one the action of the divergence synergy. The algebraic sum of the actions of the two gives the resultant motor imbalance that causes the actual fixation disparity.

When prisms are placed before the subject's eyes base-out to force an increased convergence, the convergence component responds completely, but, depending upon the particular subject, the divergence component may not relax proportionally but may resist increasingly the movement demanded by the prisms in accordance with the innervations from the accommodation-convergence reflex. Conversely, if the prisms are placed base-in, it is the convergence component that tends to resist the movement.

Now the shape of each of these two components obviously is not due entirely to the behavior of the convergent muscular synergy alone or the divergent muscular synergy alone, for each must also include the restraining anatomic or mechanical limitations of the disjunctive movements of the eyes. Moreover, the particular behavior of each will reflect the resultant innervation of the accommodation-convergence reflex, as that reflex reacts to the effect of the prisms and to the observation distance.

The chief value of this two component concept is that it provides an explanation of the second type of fixation disparity curve. Clearly, if one of the synergies is inoperative, only the other remains. The data found in curves as shown in G and H, Figure 4, are examples. These curves are displaced vertically, and this displacement must indicate basic and neurogenic imbalances (heterophoria) and is not due to a positive functional muscular synergy. The opposing synergy is purely passive.

It may be suggested that in this type of curve the eyes actually voluntarily accommodate under the compulsion of the accommodation-convergence reflex, as the conver-

gence is changed by the prisms; accordingly there is an accommodative convergence impulse that eliminates or reduces the muscular imbalance. In some of the curves this is undoubtedly true, and perhaps to some extent it occurs in all curves of this type. However, the accommodative change could not be as large as that demanded over the range; otherwise the vision would be so blurred that the subject could not discriminate the test detail.

The third type of curve (I and J, fig. 4), which occurs more rarely, has been found in individuals with disturbed binocular coördination. We must attribute it to some extent to a breakdown of both of the muscular synergies, and in turn this may result from a subnormal accommodation-convergence reflex. At least this reflex seems to operate only in a very limited range; the images readily blur and the prism convergence and divergence are almost unresisted.

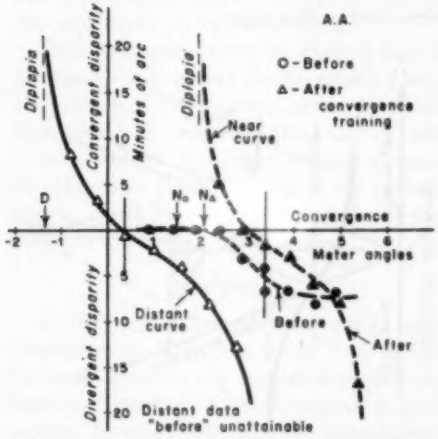

Fig. 13 (Ogle and Prangen). An example which shows that the third type of fixation disparity curve is susceptible to convergence and fusion (?) training.

The binocular coördination of the eyes of an individual with such curves seems to be subject to training, as is illustrated in Figure 13. For this subject, at the first examination, no curve for distant vision could be obtained at all, and the near curve was of this third type. After some two and a half months of convergence training under the supervision of an orthoptist, normal type curves were found both for distant and near observation distances. The initial divergent fixation disparity was decreased, but the phorias were little changed.

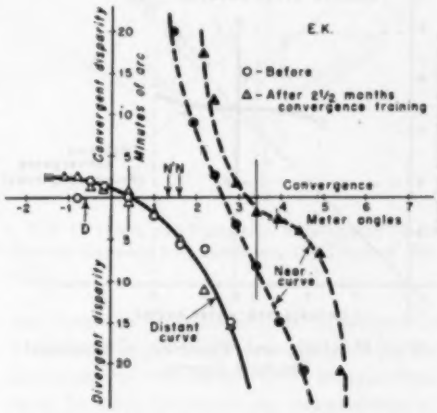

Fig. 14 (Ogle and Prangen). The effect of convergence training on a subject with mixed types.

Figure 14 illustrates the data of a subject with mixed first and second types for distant and near vision. Two sets of data are shown, one obtained before and the other after two and a half months of convergence training conducted by an orthoptist. The distant vision (second type) curve remains unchanged. At near vision the initial fixation disparity is greatly reduced, and, while the prism vergence amplitude is not greatly increased, the slope of the curve in the active region is considerably reduced.

In these cases it is difficult to determine whether the training has affected the accommodation-convergence reflex or the compulsion to fusion reflex. For this subject the latter might be the case since the distant curve has been unaffected.

5. Relationship of the fixation disparity curves to Donders' diagram. Donders' diagram (fig. 15) is a graphic representation

of the accommodation and convergence functions. This diagram has been useful in studying the association between the relative accommodation and relative convergence. In the usual chart the absolute convergence corresponding to the observation distance is

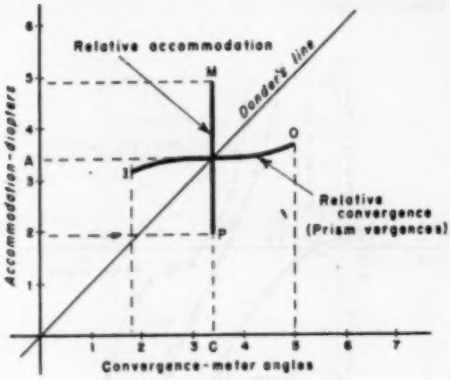

Fig. 15 (Ogle and Prangen). Conventional Donders' diagram.

plotted in meter angles (sometimes prism diopters or centrads) on the abscissa (X). The accommodation of the eyes is plotted in diopters on the ordinates (Y).

Under normal conditions we should expect the accommodation to keep pace exactly with the convergence demanded by the distance of the object observed. This relationship would be indicated on the chart by the line at a 45 degree angle—a line known as Donders' line.

For a given object distance and the corresponding convergence (C), there would be an accommodative state A. If now the observer is subjected to the prism vergence test, prisms of increasing power, base-in, are interposed before the eyes; the eyes increasingly diverge under their influence, until blurring or diplopia or both occur (designated by point I on the chart); prisms of increasing power base-out force the eyes to converge, until again blurring or diplopia or both occur (indicated by point O). During this process the accommodation changes little, but it probably does change to the extent of the depth of focus of the eyes, so that the representative curve would be a slightly reverse curve as shown.

During the prism vergence test the subject increasingly experiences a "strain in the eyes" and a resistance to the prisms as the prism power is increased. Now it is this resistance or tonicity difference between the convergence and divergence muscular synergies that is measured in the fixation disparity curves.

These data can therefore be coupled to Donders' diagram by making the chart three dimensional by adding a Z axis and plotting the fixation disparity on it (fig. 16). Above the plane of this diagram we can plot the convergent fixation disparity, and below the plane the divergent fixation disparity measurement. Thus the curve in the plane determined by the convergence X and by the fixation disparity Z axes illustrates the data described in this paper.

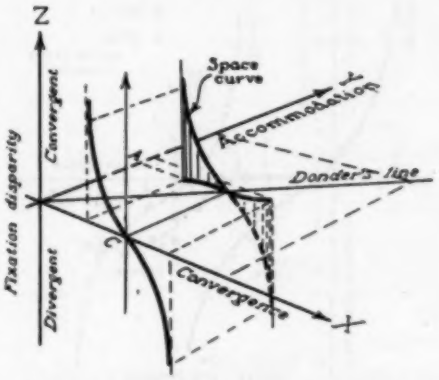

Fig. 16 (Ogle and Prangen). Relationship of the fixation disparity-prism vergence curve and the Donders' diagram.

This curve is obviously the projection on the X Z plane of a space curve, just as the reverse curve of Donders' chart is also a projection of that space curve on the X Y plane.

In a similar manner the relative accommo-

dation is determined by adding positive and negative spheres before the eyes. In Figure 15, for the convergence C, when negative spheres are added the eyes accommodate to a limiting value N, when blurring occurs; when positive spheres are added the accommodation relaxes to a limiting value P, when blurring again occurs.

With the process of increased and decreased accommodation, there will be the change in the muscular imbalance through the accommodation-convergence association, and a change in the fixation disparity occurs. This change can be graphically represented in the same three dimensional figure as shown in Figure 17.

This diagram is the same as Figure 16 except that it has been rotated so that we look more directly upon the Y Z plane. On this plane is the fixation disparity-accommodation curve (compare fig. 9). Again this curve is the projection on the Y Z plane of a space curve, just as the line NP is a projection of the same curve on Donders' chart.

These two space curves of Figures 16 and 17 are obviously curves that determine a surface in space. This surface cannot be easily represented in a figure. This surface will vary in position and shape depending upon the particular characteristics of the heterophoria, prism vergence amplitudes, and the subject's fixation disparity pattern.

Comment

At the present time probably not enough measurements have been made from which we could evaluate the importance of these fixation disparity curves in routine clinical testing. In many instances the information conveyed by these curves might be obtained from the carefully performed prism vergence tests when studied in conjunction with the other ocular data on the patient. This is probably not so in other instances.

The behavior pattern of the response to prisms (or lenses) may be entirely different in two different subjects with identical prism vergence limits. In the one a highly developed fusion power may be indicated; in the other a poorer one, as would be suggested by the slope of the curve.

While an initial fixation disparity is certainly an indication of a motor imbalance,

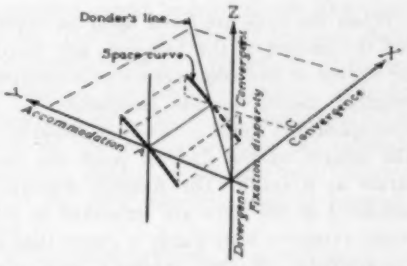

Fig. 17 (Ogle and Prangen). Relationship of the fixation disparity lens curve and the Donders' diagram.

and even the direction of that imbalance, its magnitude is not highly correlated with the heterophoria measured with disassociated eyes. In many instances the measurement of heterophoria gives a misleading indication of the motor imbalance when the eyes are associated with fusion. Especially is this true in certain of the intermittent or possible tropias. We cannot say that the existence of a fixation disparity is *per se* an indication of a source of eye strain any more than the phoria alone. However, the data tend to support the thesis that in normally coördinating eyes, the fixation disparity is small, as is the heterophoria.

These fixation disparity curves may provide a clue as to why small degrees of prisms may greatly benefit one patient, and a large prism may not help another. For example, in Figure 3-F, where the fixation disparity changes rapidly with prism power, a small prism will greatly reduce the disparity. On the other hand, in Figure 4-J, distant vision curve, no amount of prism power base-in will reduce the disparity to zero.

The chief value of these data lies in their providing a background to one's understand-

ing more about the processes involved in binocular single vision. Certainly any series of measurements that are reliable and that show patterns characteristic of the individual must have significance.

Summary

When the eyes are fixed upon an object and the images in the two eyes are fused, the degree of overconvergence or underconvergence caused by the compulsion of a heterophoria is called a "fixation disparity." The images of the fixation point are disparate as a result. The fixation disparity, measured as the eyes are subjected to the prism vergence test, yields a curve that is characteristic of this subject's particular ocular behavior. Three different patterns of such behavior are found in a group of subjects.

The magnitude of the normal fixation disparity, while usually in the same direction as the heterophoria, correlates poorly, because the magnitude of the disparity depends not alone on the heterophoria but also on the particular fusional behavior pattern. The heterophoria with fusion is indicated by that prism vergence for which the fixation disparity is zero. A fair correlation exists between the heterophoria with eyes disassociated and when fusion is maintained, but in many instances the phoria with eyes disassociated gives a false measure of that actually existing with fusion.

A hypothesis based on the data is made that the strength of the fusion compulsion reflex is maximum when the disparity of the retinal images is near the doubling point. This strength decreases as the images fall nearer corresponding retinal points. The accommodation-convergence association and the reflex to the accommodative mechanism to preserve clear images are related to the fixation disparity curves. It is shown that this relationship is essentially linear.

The general fixation disparity curve is shown to consist of two components that can be attributed to the convergence and divergence synergies of the extraocular muscles of the eyes.

The fixation disparity curves obtained with prism vergences are related to the usual Donders' chart by plotting the fixation disparity measurements on a third dimension.

Mayo Clinic.

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EFFECT OF ACTH AND CORTISONE ON OCULAR DISEASE*

MICHAEL J. HOGAN, M.D., EPHRAIM P. ENGELMAN, M.D., PHILLIPS THYGESON, M.D., AND MARCUS KRUPP, M.D.
San Francisco, California

The original discovery by Hench, *et al.*[1] that cortisone (compound E, 17-hydroxy-11-dehydro-corticosterone), an adrenal cortical steroid, and pituitary adreno-corticotropic hormone (ACTH) induced marked improvement in patients with rheumatoid arthritis has led to a new approach in the management and study of a number of diseases.

Thorn, *et al.*[2] noted a similar improvement with ACTH in patients with rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, and gout. Thorn and his group of workers pointed out that rheumatic fever, disseminated lupus erythematosus, and rheumatoid arthritis are related mesenchmyal diseases, characterized by a nonspecific inflammatory reaction, brought on by a peculiar susceptibility of the host to certain bacterial or tissue products, and that such states appear to be benefited by a sudden increase in titer of the circulating 11, 17-oxysteroids.

A number of articles have since appeared on the effects of both ACTH and cortisone in rheumatoid arthritis and other diseases. All observers agree that these substances produce rapid remissions in such diseases as rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, and status asthmaticus. In most instances a relapse occurs within a short period after cessation of treatment. It has also been noted that serious complications may accompany their use. Prolonged administration may result in Cushing's syndrome. Observations must be made for evidence of electrolyte derangement or water retention.

It was natural that, since rheumatoid arthritis is often associated with uveitis, these hormones should be tried in the latter condition. The eye is an ideal place to study inflammations because the effects of the inflammation are easy to observe and the healing process can be carefully controlled with the slitlamp microscope and ophthalmoscope. Biopsy, which has been resorted to in the joint manifestations, is unnecessary.

Rheumatoid arthritis is accompanied by uveitis in from two to five percent of cases. Approximately 20 percent of patients with Still's disease (juvenile rheumatoid arthritis) may develop uveitis, and from 15 to 50 percent of patients with rheumatoid arthritis of the spine (Marie-Strümpell's disease) are said to develop a uveitis.[3]

Reports have already appeared dealing with the effect of ACTH in ophthalmic conditions—Gordon and McLean,[4] Olson *et al.*,[5] and Mann and Markson.[6]

This study, as yet incomplete, was undertaken to evaluate the effect of both ACTH and cortisone in the following conditions: (1) Acute and chronic rheumatoid uveitis, (2) acute and chronic nonrheumatoid uveitis, (3) granulomatous uveitis, (4) allergic corneal and conjunctival disease (vernal catarrh, phlyctenulosis, and so forth).

Detailed studies have been made upon seven cases, and the ocular findings are presented. The metabolic changes and clinical course of these patients from a standpoint of their general disease (rheumatoid arthritis, atopic dermatitis, and so forth) will be presented in a subsequent report.

The following groups of cases have been studied: (1) Chronic rheumatoid uveitis, one case; (2) acute rheumatoid uveitis, two cases; (3) chronic recurrent granulomatous uveitis, one case; (4) acute nongranuloma-

* From the Division of Ophthalmology, Francis I. Proctor Laboratory for Research in Ophthalmology, and the Division of Medicine, University of California School of Medicine, and from the San Francisco Veterans Administration Hospital. This work was supported by a grant from the Snyder Ophthalmic Foundation.

tous uveitis and papillitis, one case; (5) atopic keratoconjunctivitis and dermatitis, one case; (6) vernal catarrh, one case.

In all instances the patients were hospitalized, and the necessary preliminary clinical and laboratory studies were carried out before instituting therapy. These cases had been observed for a sufficient period prior to therapy to establish a base-line of activity. No specific or nonspecific treatment was given after commencement of the hormones, other than atropine or scopolamine for the uveitis cases, except as indicated in the case reports.

Case reports

Rheumatoid uveitis

The uveitis which accompanies rheumatoid arthritis occurs in both an acute and chronic form, and seems to be much more common in those patients with a spondylitis. Characteristically only an iridocyclitis occurs.

The acute type comes on suddenly, in one or both eyes, and exhibits intense congestion, moderate keratitis, and a heavy aqueous flare with many cells. Not infrequently a fibrinous coagulum is seen. Keratic precipitates are usually small, granular, gray-white, and adhere to the lower cornea.

The inflammation lasts 15 to 45 days, but may disappear earlier if treatment is instituted. Usually the attacks recur at varying periods, and may be followed by a chronic phase in which the ciliary body is principally affected and large numbers of anterior vitreous opacities appear. This form may last for years, and exhibits the exacerbations and remissions which are noted in the joints.

Case 1

Chronic rheumatoid uveitis. (Case 1.) A. L., aged 32 years, a white man, research chemist, had chief complaints of (1) generalized arthritis of nine years' duration and (2) bilateral inflammation of the eyes of two years' duration.

History. The patient had been in good health until 1940 when he developed a recurring pain in the left hip. By 1942, the lower back, thoracic spine, hips, and shoulders were involved in a typical rheumatoid athritis.

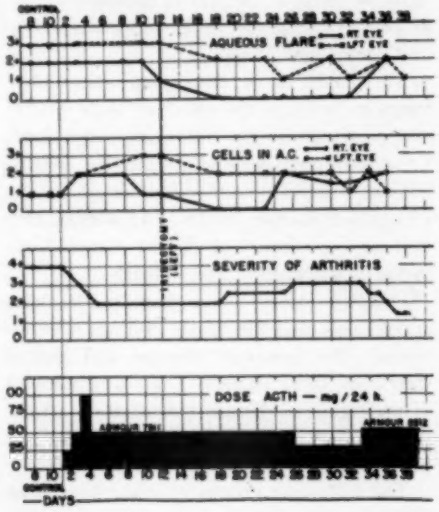

Chart 1 (Hogan, *et al.*). Chronic uveitis in rheumatoid arthritis. Response to ACTH (A. L., December 8, 1949).

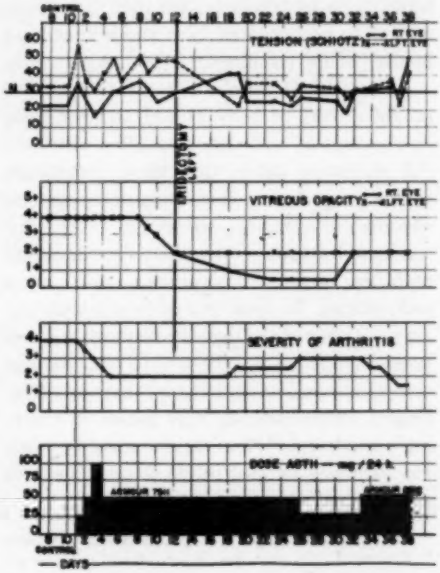

Chart 2 (Hogan, *et al.*). Chronic uveitis in rheumatoid arthritis. Response to ACTH (A. L., December 8, 1949).

An acute left iridocyclitis of short duration appeared in this year. It recurred in 1945 on two occasions. The arthritis became progressively disabling. In 1947, a chronic left iridocyclitis appeared and has continued to the present time.

In August, 1948, a similar type of iridocyclitis developed in the right eye and has also persisted to this time. In the interval between 1947 and 1949, there was moderate weight loss, recurring attacks of pain in various joints, and progressive disability, so that he was bedridden.

He was admitted to the University of California Hospital on May 24, 1949, under the care of one of us (E. P. E.) Supportive treatment and physiotherapy were given. A course of intramuscular adrenalin (0.5 mg. four times a day for 13 days) caused no improvement.

Eye examination. At this time vision in the right eye was 10/200 and in the left, 3/200. There was no congestion of either eye. The right eye showed a slight keratitis with a few small keratic precipitates. There was a two-plus flare and cells in the aqueous and three-plus vitreous opacities. The pupillary portion of the iris was almost totally adherent to the lens. The fundus was only very hazily seen.

The left eye showed a very slight keratitis, no keratic precipitates, a two-plus flare, and only occasional cells. Almost complete synechias of the pupillary iris to the lens were present. The left lens showed an early cataracta complicata, and the vitreous contained three-plus opacities. The intraocular pressure was normal.

In October, 1949, the eye findings were the same except that the tension measured 32 mm. Hg, R.E.; 35 mm. Hg, L.E. (Schiøtz).

In November, 1949, studies were made prior to institution of ACTH therapy. Treatment was started on December 12, 1949, and continued as shown on Charts 1 and 2. The initial adrenal response to ACTH was good, as evidenced by eosinopenia and increased output of urinary 17-ketosteroids.

Course. There was a fair response to ACTH in the ocular inflammation as well as the joints, but during the entire period of treatment the cells never entirely disappeared from the aqueous of the left eye, indicating that, despite evidence of good adrenal response to ACTH, a complete remission was not obtained. For a short period, 18th to 22nd day, they appeared to be absent from the right eye.

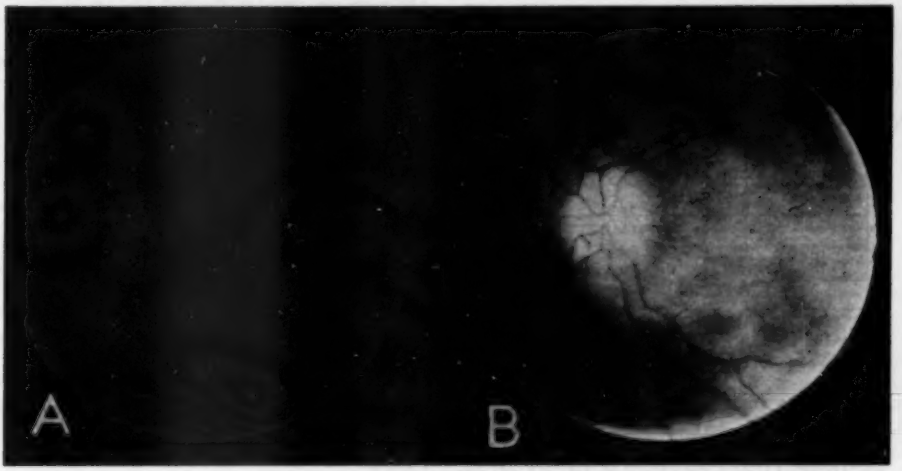

Fig. 1 (Hogan, *et al.*). Case 1. Drawing of vitreous haze and fundus before (A) and after (B) treatment to show the amount of clearing.

The ocular tension became higher in each eye as treatment was continued, but showed considerable variation, seemingly having a relationship to the iridocyclitis. The vitreous opacities cleared markedly so that a good view of the right fundus could be obtained within 12 days after instituting treatment (fig. 1).

Because of the development of iris bombé an iridectomy was done on the left eye on December 23, 1949. Healing of the wound was uneventful but the elevated ocular tension was unaffected. The patient showed a gradually decreasing response to ACTH therapy as evidenced by an increase in the circulating eosinophils and decrease in 17-ketosteroid output. At the same time there was a gradual recurrence of the joint symptoms and ocular inflammation.

ACTH was discontinued on February 5, 1950. On February 8, 1950, the iridocyclitis of both eyes was active again and the ocular tension was decreasing rapidly. By February 10th, the intraocular pressure

in the left eye was so low that it could not be recorded with a tonometer.

In view of the previous evidence of decreasing adrenal response to ACTH, it was decided to determine the effects of cortisone which was started on February 23, 1950. The dosage and results are seen in Chart 3. The response initially to larger doses was good, and upon a daily dose of 100 mg.

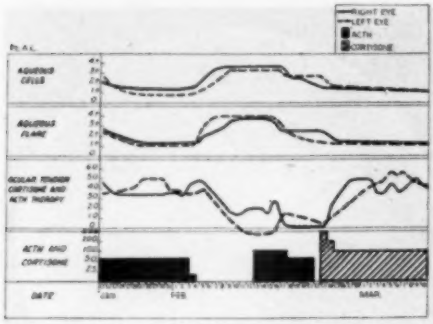

Chart 3 (Hogan, *et al.*). Rheumatoid uveitis. Cortisone and ACTH therapy (A. L.).

the eyes and joints showed moderate gradual improvement. The treatment was discontinued on March 27th for eight days, started again on April 4th (chart 4), and continued to the day of discharge from the hospital, May 19th. He has been maintained on intermittent treatment as an outpatient since that time.

It can be seen from Chart 4 that the iridocyclitis in his left eye subsided almost completely, but the

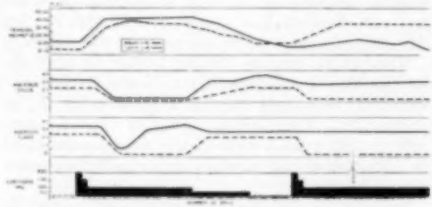

Chart 4 (Hogan, *et al.*). Rheumatoid uveitis with secondary glaucoma. Response to cortisone (A. L.).

tension rose simultaneously. During this same period the right eye failed to improve. The joints showed moderate improvement. A cyclodialysis was done on the left eye without complication on April 24th but had no effect on the intraocular pressure.

Comment. The response to ACTH was only fair, and possibly the poor result was due to a decrease of adrenal response. Of interest was the rise in ocular tension in each eye with treatment, and subsidence of the iridocyclitis. We have seen no other cases in which the tension became elevated during treatment so are inclined to attribute the increased pressure to a remission of the iridocyclitis.

Upon recurrence of the iridocyclitis after cessation of treatment the ocular tension in both eyes dropped rapidly to subnormal levels.

Cortisone in a dose of 100 mg. a day caused improvement in the joint symptoms and the left eye became almost, but not entirely, uninflamed. The right eye failed to respond.

We feel this patient obtained only an incomplete response in his eyes to ACTH and cortisone therapy. The explanation for this failure may be that inadequate treatment was given.

An iridectomy and a cyclodialysis were done dur-

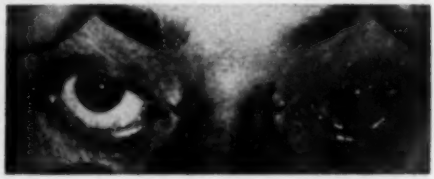

Fig. 2 (Hogan, *et al.*). Case 2. Acute rheumatoid iridocyclitis. Right eye prior to treatment.

ing the course of treatment, without complication or interference with wound healing.

CASE 2

Acute rheumatoid uveitis. (Case 2.) A. E., aged 29 years, a white man, a student, presented the chief complaints of (1) acute inflammation, right eye, 26 days, and (2) arthritis, eight years.

Past history. The patient developed an arthritis of the left shoulder, lower back, and sacro-iliac region in early 1941, with some permanent limitation of motion. In 1942, he had an exacerbation of the hip, shoulder, and back pain with fever, lasting two weeks. By October, 1946, he had developed the picture of definite rheumatoid joint disease with involvement of the larger joints and a spondylitis.

During October, 1947, he developed an acute left iritis and was treated with typhoid injections, atropine, and gold-salts.

Examination in January, 1949, showed involvement of all the vertebral joints with restricted motion. X-ray therapy afforded moderate relief. The sedimentation rate remained constantly elevated.

Present history. On December 14, 1949, he developed an acute inflammation of the right eye. Examination the following day showed an acute iridocyclitis, keratitis, a heavy aqueous flare and cells, and a few tiny keratic precipitates. The vision was 20/40. He was sent to the San Francisco County Hospital where he was given intravenous typhoid vaccine, salicylates, and atropine. After one week he was considerably improved and was referred back to the University of California Clinic. The iridocyclitis again became acute (fig. 2) and

failed to respond to ordinary outpatient measures.

He was admitted to the hospital on January 11, 1950, for cortisone treatment. Preliminary laboratory studies were made and treatment was started on January 12th. The dosage and response are shown on Chart 5.

Course. The response to treatment was rapid and within one week the cells and flare had diminished considerably. Thereafter there was slow improvement up to the day of discharge on January 30th (18th day of treatment). Very occasional cells and a faint aqueous beam were present on the day of discharge. The dosage was gradually reduced and treatment was discontinued on February 4, 1950.

The arthritis showed a corresponding, but more rapid improvement, and most of the stiffness and

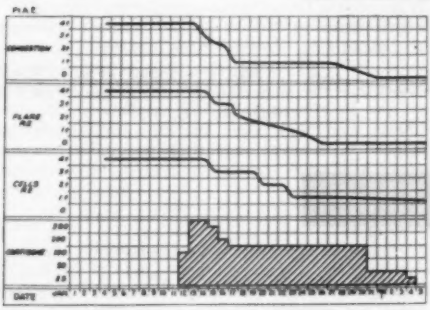

Chart 5 (Hogan, *et al.*). Effect of cortisone on rheumatoid iridocyclitis (right eye of Patient A. E.).

pain had disappeared from the affected joints within two weeks.

On February 6, 1950, the right iridocyclitis recurred, accompanied by pain, marked congestion, a heavy aqueous flare, and fibrin clot. A slight flare and occasional cells were also noted in the left eye, which had previously been unaffected.

Salicylates, atropine drops, and compresses were ordered, and the inflammation gradually subsided. The subsequent course is seen in Chart 6. He was last seen on March 25, 1950. At that time a very occasional cell was noted in the aqueous of the right eye and vision was 20/20.

Comment. The acute rheumatoid iridocyclitis in this patient responded rapidly to cortisone treatment but, after 23 days' treament, there was still evidence of low-grade activity in the eye. It is possible that treatment should have been continued, but we were interested at this time in the response of acute uveal inflammation to cortisone. The recurrence and prolonged course after cessation of treatment, with activation of an iridocyclitis in the previously normal left eye suggests that exacerbations may be followed by a more extended period of activity and reactivation of formerly quiescent lesions.

This patient at no time developed any side effects from use of cortisone.

CASE 3

Acute rheumatoid uveitis. (Case 3.) G. J., aged 34 years, a white man, an accountant, had, as chief complaints, (1) acute inflammation right eye, two days; (2) arthritis, eight years.

Past history. The patient developed an arthritis

Pt. A.E.

DATE	CONGESTION	AQUEOUS FLARE	AQUEOUS CELLS
Feb 6	4+	4+	4+
9	4+	4+	2+
12	4+	3+	2+
15	2+	3+	1+
18	2+	2+	1+
21	2+	2+	1+
24	2+	1+	1+
27	1+	0-1+	1+
Mar 1	0-1+	0-1+	2+
4	1+	0-1+	1+
7	1+	0-1+	1+
10	2+	1+	1+
13	2+	1+	1+
16	2+	2+	2+
19	2+	2+	2+
22	1+	2+	1+
25	1+	1+	1+
28	0	0	0
31	0	0	0

Chart 6 (Hogan, *et al.*). Course of iridocyclitis, right eye, after discontinuing cortisone (A. E.).

of the lower spine in 1942. Within the following year the entire spine was affected. He was given 10 gold injections, which allegedly caused some amelioration of symptoms.

An attack of acute iridocyclitis occurred in each eye during 1943. A severe recurrence developed in the right eye in 1948 with macular edema. As the iridocyclitis subsided, the vision was found to be lowered due to a dense small central scotoma. The best obtainable vision was 20/70.

Present history. On February 4, 1950, an acute attack of iridocyclitis occurred in the right eye. It gradually subsided by March 15th, but the aqueous continued to show a faint flare and occasional cells.

An acute iridocyclitis developed in the left eye on April 7, 1950. Vision was reduced to 20/60. In addition to the typical findings associated with the

iridocyclitis, fundus examination showed a faint gray-white area of macular edema. He was admitted to the hospital on this day for ACTH therapy. After study, treatment was instituted on April 11, 1950.

Course. The dosage of ACTH and results of treatment are recorded in Chart 7. A good adrenal response to ACTH was obtained. Marked amelioration of joint symptoms occurred within a few days. The iridocyclitis in the left eye cleared rapidly, vision improved to 20/20, and only an occasional cell could be seen in the aqueous at the end of 12 days.

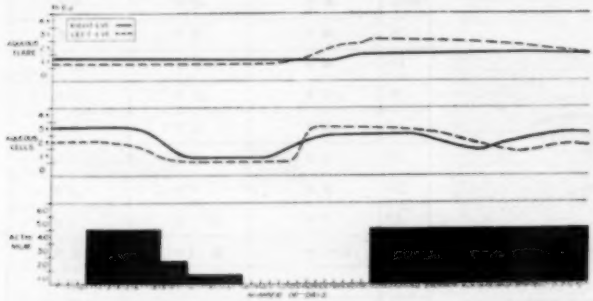

Chart 7 (Hogan, *et al.*). Rheumatoid uveitis. Response to ACTH treatment (G. J.).

The right eye also continued to show low-grade activity and, after 17 days' treatment, ACTH was discontinued. The iridocyclitis became more acute in both eyes after one week and continued active in the ensuing days.

ACTH in a dose of 40 mg. daily was again started on May 12th and continued until June 2nd with poor adrenal-cortical response and with but very little effect on the iridocyclitis. A different lot of ACTH was received and started on June 2nd in a dose of 60 mg. daily. This was followed by a good adrenal response. Within three days the iridocyclitis showed improvement, with a decrease in the cells and flare in the aqueous of both eyes. On June 16th, he still showed one-plus cells and flare in each eye.

Comment. Definite improvement in both the eyes and joints was obtained during the first course of ACTH but a complete remission of signs was never obtained in either eye in spite of evidence of a good adrenal response. A prompt relapse occurred within a week after cessation of treatment. A second course of treatment probably failed to result in improvement because of inadequate dosage, or an impotent batch of ACTH.

A change to a different lot of ACTH in a larger dose caused marked improvement within three days but failed to cause complete subsidence of the iridocyclitis in 14 days. The only side effect noted during treatment was a decided euphoria.

CASE 4

Chronic recurrent granulomatous uveitis. (Case 4.) M. N., aged 47 years, a white housewife, presented the chief complaints of (1) recurrent iridocyclitis with secondary glaucoma, eight years; (2) progressive muscular weakness, four years.

Past history. In 1942, the patient noted bilateral blurring of the vision, and was treated for an iridocyclitis, left eye. Recurrent attacks were noted up to 1945, when pain developed in the left eye, and a diagnosis of secondary glaucoma was made. In 1946, a similar condition developed in the right eye. Complete examination showed no cause for the uveitis. Tuberculin, typhoid vaccine, streptomycin, and antihistaminics had no effect. Attacks of iridocyclitis and secondary glaucoma developed every six months to a year after 1946.

In 1948, the tension was uncontrolled and a trephination was done on both eyes. In early 1949, the left eye was red, painful, and blind, so it was enucleated. Histologic examinations showed only a nonspecific granulomatous inflammation.

The right eye continued to develop occasional low-grade attacks of iridocyclitis, and elevation of tension. Between attacks, the pressure remained normal with the use of pilocarpine.

Numbness and weakness of the right arm and difficulty in walking developed in 1946. She was examined by clinicians and neurologists who felt the changes were on a degenerative basis. No specific diagnosis could be made, except that the cord was the chief location of the disorder. Electromyographic studies showed no evidence of lower motor-neuron disease.

The patient was referred for treatment by Dr. Frederick C. Cordes and Dr. Yale Brody to whom we are indebted for permission to present the findings in this case.

She was admitted to the University of California Hospital on March 9, 1950.

Eye examination. Vision in the right eye was 20/100 without correction and 20/100 with correction. The eye was not congested. The cornea showed a circular scar near the 6-o'clock position due to a previous ulcer. The aqueous showed a two-plus flare and cells and there were five mutton-fat keratic precipitates inferiorly. An iridectomy was present superiorly, and the trephination was not func-

tioning. The lens showed some posterior subcapsular opacification, and the vitreous was hazy due to fine anterior dustlike opacities. The fundus appeared normal. Tension was 30 mm. Hg (Schiøtz).

After study, cortisone was started on March 20, 1950. The dosage and results are shown on Chart 8.

Comment. We were interested in this case because of the presence of a granulomatous uveitis, accompanied by secondary glaucoma. Experience with another case in this series (Case 1, A. L.) showed that, as the uveitis subsided the intraocular pressure rose. A similar change did not occur here, so it is likely the water retention which may occur on administration of cortisone plays no part in the production of glaucoma.

The uveitis promptly subsided after institution of cortisone therapy, but the possibility exists that it may have regressed spontaneously. This patient remained entirely well until June 13, 1950, when examination showed two-plus cells and a one-plus flare in the aqueous. She was unaware of any recurrence. Local cortisone drops (cortisone acetate suspension diluted with two volumes of normal saline) were ordered on this day to be used in the eye every hour.

CASE 5

Acute nongranulomatous uveitis and papillitis. (Case 5.) M. Mc., aged 12 years, a white schoolgirl, had, as a chief complaint, bilateral inflammation of the eyes of five weeks' duration.

History. The patient had a cold and sore throat lasting 10 days in late February, 1950. On March 4, 1950, she developed discomfort and redness in the eyes. Examination showed a conjunctivitis, and local treatment was instituted. Two weeks later there was bilateral pain and increasing redness and a diagnosis of acute iridocyclitis was made. Complete physical examination, including X-ray films of the chest, hands, sinuses, and wrists, was negative.

She was given three intramuscular injections of typhoid vaccine, aureomycin by mouth, p-aminosalicylic acid, streptomycin intramuscularly, and atropine drops. Vision was steadily decreasing after two weeks and the uveitis became progressively worse.

She was referred to the uveitis clinic at the University of California Hospital. We are indebted to Dr. Dudley Bell for permission to present the findings in this case.

Eye examination showed a bilateral acute uveitis and papillitis. Vision in the right eye was 20/60 and in the left eye, light perception. There was marked blepharospasm, edema of the lids, extreme photophobia, and congestion of the conjunctivas. The corneas were hazy and a heavy fibrinous exudate was present in the aqueous.

The vitreous of the left eye contained so many cells the fundus could not be seen. However, examination a few days earlier had shown a papillitis in this eye.

The vitreous of the right eye also contained many cells, but the fundus could be observed. The disc was edematous, elevated, and congested, and there was a small exudate and hemorrhage on its upper nasal surface.

She was admitted to the hospital on April 15, 1950, for cortisone treatment. Treatment was instituted on April 19, 1950. The dosage and course of the inflammation are given on Chart 9.

P. M. N.

DATE	CORTISONE MG	AQUEOUS FLARE	AQUEOUS CELLS	TENSION (SCHIOTZ) R.E.	VISION R.E.
Mar 9		2+	2+	30	20/100
15		2+	2+	29.5	
20	150	1+	1+	42	20/100
21	300	1+	1+	30	10/200
22	100			35	
23	100	1+	1+	30	
24	100	0	0	37	
25	100	0	0	41	
26	100			49	
27	100	0	0	32	
28	100			31	
29	100	0	0	40	
30	100			30	
31	100			37	
Apr 1	100	0	0	25	
2	100			27	
3	100			27	
4	100	0	0	28	
5	100				
6	100	0	0	28	20/10-1
7	100				
8	50	0	0		
9	50			25	
10	50	0	0		
11	50				
12	50	0	0	30	
13	0	0	0		

Chart 8 (Hogan, *et al.*). Recurrent uveitis with secondary glaucoma. Response to cortisone (M. N.).

Course. The dosage of cortisone was gradually decreased and discontinued on May 7, 1950. At this time except for a few fine vitreous opacities and slight evidence of papillitis in the left eye she appeared entirely well, and was discharged from the hospital.

On May 10, 1950, the left eye again developed an acute iridocyclitis with vitreous opacities. Salicylates and fever therapy were given. Since that time, there have been intermittent acute outbursts of iridocyclitis in each eye, but without activation of the papillitis.

Comment. The response of this case of acute bilateral uveitis and papillitis to cortisone was prompt and satisfying; however, a permanent remission of the disease was not obtained. The inflammation re-

curred within four days after cessation of treatment.

An interesting observation was the rapidity with which the vitreous opacities disappeared after institution of therapy. It is possible that, if treatment had been continued for several more weeks, the patient may have been carried into a state of remission. No physiologic alterations were noted during the course of treatment.

CASE 6

Atopic keratoconjunctivitis and dermatitis. (Case 6.) E. C., aged 47 years, a white, drug manu-

DATE	CORTISONE MG	CELLS		FLARE		CONGESTION		VITREOUS OPACITIES		PAPILLITIS		VISION	
		R	L	R	L	R	L	R	L	R	L	R	L
Apr 13		4+	4+	4+	4+	4+	4+	3+	4+	4+	4+	5/60	LP
15		3+	3+	4+	4+	4+	4+	3+	4+	4+	4+		
17		3+	3+	4+	4+	4+	4+	3+	4+	4+	4+		
19	200	3+	3+	3+	3+	3+	3+	3+	4+	4+	4+		
21	200	1+	1+	3+	3+	2+	2+	2+	4+	4+	4+	5/60	LP
23	100	1+	1+	2+	2+	1+	1+	1+	2+	3+	3+		
25	100	1+	1+	0→+	1+	0	0	1+	1+	3+	3+		
27	100	1+	1+	0	0	0	0	1+	1+	2+	2+	5/60	5/60
29	100	1+	1+	0	0	0	0	1+	1+	2+	2+		
May 1	100	1+	1+	0	0	0	0	1+	1+	1+	2+	5/60	5/60
3	100	1+	1+	0	0→+	0	0	1+	1+	1+	1+		
5	100	1+	1+	0	0→+	0	0	1+	1+	1+	1+		
7	100	1+	1+	0→+	0→+	0	0	1+	1+	1+	1+	5/60	5/60
9	100	0→+	0	0	0	0	0	1+	1+	1+	1+		
11	100	0	0	0	0	0	0	1+	1+	0	1+		
13	100	0	REC.	0	0	0	0	1+	1+	0	1+		
15	100	0→+	0→+	0	0	0	0	1+	1+	0	1+		
17	100	0	0	0	0	0	0	1+	1+	0	1+	5/60	5/60
19	100	0	0	0	0	0	0	1+	1+	0	1+		
21													

Chart 9 (Hogan, *et al.*). Bilateral acute uveitis and papillitis. Response to cortisone (M. Mc.).

facturer, had the chief complaints of poor vision, keratoconjunctivitis, and dermatitis of seven years' duration.

Past history. At the age of 15 years, he developed mild attacks of hay fever, rhinitis, and occasional asthma, of a nonseasonal type. His mother and one daughter have asthma, the latter in association with colds.

During 1942, the left eye became inflamed, with burning, tearing, and itching. He was treated by a number of physicians without benefit. He was examined by an allergist in March, 1944, and found sensitive to 10 ingestants, five environmentals, 22 pollens, and house dust.

Desensitization over a period of two months afforded some relief from the ocular inflammation. In April, 1944, slight symptoms appeared in the right eye.

In September, 1944, vision in each eye was 20/25 corrected. The skin of the lids was red and thickened and the palpebral and bulbar conjunctivas were inflamed. Circumcorneal injection was present and a slight inflamed ridge was seen at the limbus of both eyes.

The slitlamp microscope showed numerous punctate staining areas in the epithelium of the cornea. A fine diffuse opacification was noted at the level of Bowman's membrane, more on the left eye. Cultures showed pathogenic staphylococci, and smears showed rare eosinophils from the left conjunctiva.

Local treatment and systemic administration of penicillin, sulfonamides, and so forth were without effect.

From this time on, his inflammatory eye and skin condition was progressive, with exacerbations and remissions.

He was first seen at the University of California Hospital on February 11, 1948, having been referred by Dr. Frederick C. Cordes, to whom we are indebted for permission to publish this case report.

At that time the right vision was 15/200; left, 10/200. The lids of both eyes were thickened, scaly, and hyperemic. The conjunctivas were inflamed and hypertrophic, with considerable mucous discharge. Both corneas were partially opaque and vascularized (figs. 3 and 4).

General physical examination showed a scaly

Fig. 3 (Hogan, *et al.*). Case 6. Condition of cornea and conjunctiva of right eye on February 11, 1948.

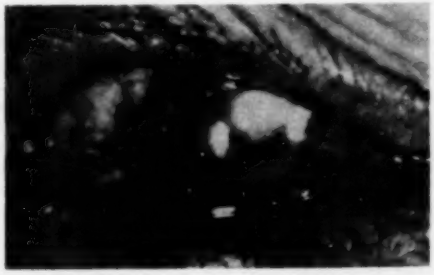

Fig. 4 (Hogan, *et al.*). Case 6. Condition of cornea of left eye on February 11, 1948.

eczematoid dermatitis of the arms, neck, forehead, ears, groin, and popliteal areas.

Conjunctival cultures showed pathogenic Staphylococcus aureus in large numbers. Scrapings showed many eosinophils. Treatment with antibiotics afforded great symptomatic relief and he was discharged improved on March 19, 1948.

Following discharge he was followed by Dr. Cordes and one of us (P. T.). Aureomycin topically and by mouth caused no improvement. It was impossible to rid the conjunctiva of the staphylococci or eosinophils.

Present history. He was readmitted on December 27, 1949. The condition of his eyes had become progressively worse and the vision was counting fingers at one foot in each eye (fig. 5). The corneas were more opaque, due to large yellow-white, deep, central opacities which were vascularized (fig. 6). The conjunctiva of both eyes was hypertrophic and congested. In addition to the hypertrophy and intense inflammation the upper tarsal conjunctivas showed many sharply defined small white scarlike lesions. As near as could be determined the lenses were clear.

Consultation with dermatologists showed some lack of agreement, but the weight of opinion favored an atopic dermatitis.

A biopsy was taken from the right upper tarsal conjunctiva on December 29, 1949. The tissue sections showed marked thickening of the conjunctiva due to infiltration of the substantia propria with granulation tissue. There was hyperplasia of the epithelium with downgrowth to form pseudoglandular structures in the granulation tissue (fig. 7).

After preliminary studies, treatment with cortisone was started on January 3, 1950. It was given daily in four divided doses, as indicated in Chart 10. Treatment was continued to March 10, 1950.

Course. There was almost immediate subjective improvement and objective changes were apparent on the fifth day. On the 10th day of treatment the dermatitis and keratoconjunctivitis were much improved (figs. 8, 9, 10, and 11). By the 12th day the conjunctival secretion and hyperemia were much less, vision was improved to reading large headlines in the newspaper, and the dermatitis was remarkably better.

The conjunctival scrapings showed no eosinophils after the 23rd day and the cultures throughout treatment were positive for pathogenic staphylococci though the number of colonies were reduced. Vision was 2/200 in the right eye after this time, but the left vision was unchanged.

The dermatitis had almost entirely disappeared at the end of a month but the vision showed no further improvement. The conjunctival mucous membrane was pale and normal appearing, except for the changes in the upper tarsal areas (fig. 12).

On February 28th (54th day) he was given chloromycetin by mouth (1.0 gm., daily), and bacitracin ophthalmic ointment locally in each eye, four times a day. The pathogenic staphylococci disappeared within a few days. At this time there

Fig. 5 (Hogan, *et al.*). Case 6. Dermatitis and keratoconjunctivitis two days after starting cortisone.

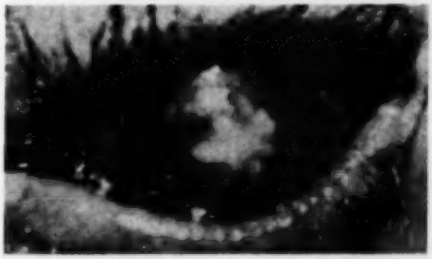

Fig. 6 (Hogan, *et al.*). Case 6. Keratoconjunctivitis of the left eye, two days after starting cortisone.

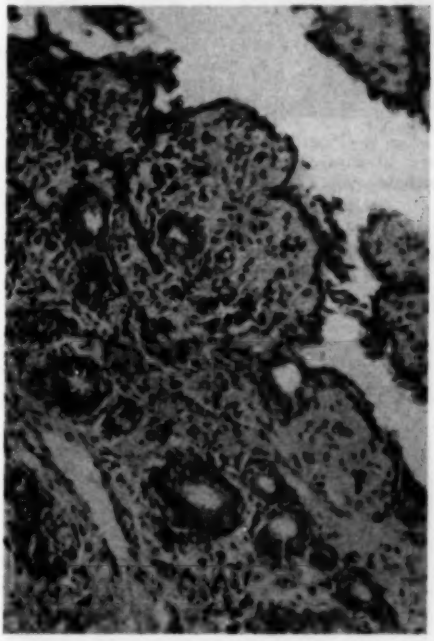

Fig. 7 (Hogan, *et al.*). Case 6. Conjunctival granuloma with pseudoglandular epithelial downgrowth.

Fig. 8 (Hogan, *et al.*). Case 6. Dermatitis and keratoconjünctivitis after 10 days of treatment with cortisone, showing marked improvement.

was an increase of the blood pressure to 150/95 mm. Hg. No other side effects were noted.

A very prompt recurrence of symptoms and signs occurred within a few days after the dose of corti-

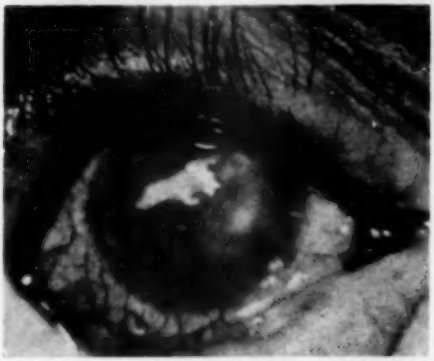

Fig. 9 (Hogan, *et al.*). Case 6. Cornea of right eye 10 days after treatment with cortisone was commenced.

sone was reduced to 50 mg. daily for one week, then 25 mg. on March 9, 1950.

It was decided to determine if a similar response could be obtained with ACTH. Forty mg. was

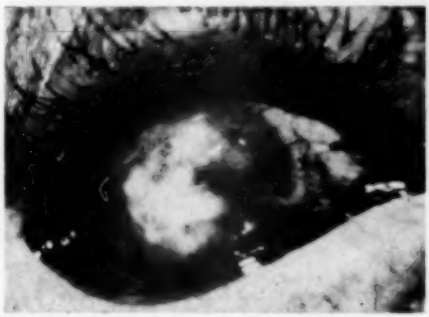

Fig. 10 (Hogan, *et al.*). Case 6. Keratoconjunctivitis, left eye, 10 days after starting cortisone.

given daily in divided doses for six days without effect. After two weeks' rest, 50 mg. ACTH was given daily for 12 days. There was very little response in any symptoms or signs, and there was an

Fig. 11 (Hogan, *et al.*). Case 6. Conjunctivitis, right eye, 10 days after starting cortisone.

absence of adrenal response to ACTH.

On April 17, 1950, 300 mg. cortisone was given; on April 18th, 200 mg., and thereafter 100 mg. daily. The response after re-institution of cortisone therapy was again gratifying, though much less rapid and satisfactory than that noted with the first course. At present the patient is receiving maintenance doses of cortisone three times weekly as an out-patient. His dermatitis is only slightly

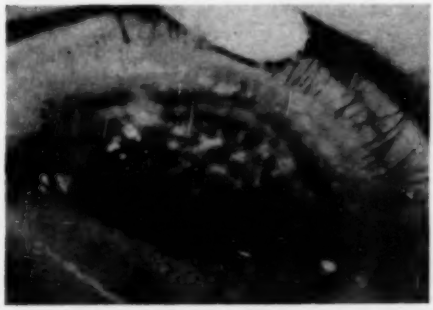

Fig. 12 (Hogan, *et al.*). Case 6. Improvement in conjunctivitis, right eye, after 27 days of cortisone treatment.

active and the conjunctivitis is moderate. Vision is unimproved.

Comment. It was not expected that vision would be improved markedly in this case in view of the permanent corneal alterations. Of interest is that the conjunctival mucous membrane returned to a normal state even though cultures showed constant

pathogenic staphylococci, and that these organisms disappeared after local use of bacitracin ointment and oral chloromycetin. Prior to cortisone treatment, these antibiotics had not significantly reduced the number of conjunctival organisms. Also of interest was the rapid disappearance of the conjunctival eosinophils on cortisone treatment.

The failure to respond clinically to ACTH is thought to be the result of failure to stimulate the

Pt: E.C.

DAY	CORTISONE MG	DERMATITIS	CONJUNCTIVITIS	CONJUNCTIVAL EOSINOPHILES	PATHOGENIC STAPH.
1	150	4+	4+	4+	4+
2	200	4+	4+	4+	4+
3	150	4+	4+	4+	4+
4	100	4+	3+	3+	4+
7	100	3+	3+	3+	3+
10	100	3+	3+	2+	3+
13	100	3+	2+	2+	3+
16	100	3+	2+	2+	3+
19	100	2+	2+	2+	2+
22	100	2+	2+	1+	2+
25	100	2+	1+	0	2+
28	100	2+	1+	0	2+
31	100	1+	1+	0	2+
34	100	1+	1+	0	2+
37	100	1+	1+	0	2+
40	100	1+	1+	0	2+
43	100	1+	1+	0	2+
46	100	1+	1+	0	2+
49	100	1+	1+	0	2+
52	100	1+	1+	0	2+
55	100	1+	1+	0	CHLOROMYCETIN BACITRACIN 1+
58	50	1+	1+	0	0
61	25	1+	1+	0	0
64	25	1+	1+	1+	0
67	0	1+	1+	1+	0
70	0	2+	1+	2+	1+
73	0	2+	1+	3+	1+
76	0	3+	2+	3+	2+
79	0	3+	2+	3+	2+

DAILY DOSE DURING THIS PERIOD

Chart 10 (Hogan, *et al.*). Atopic keratoconjunctivitis and dermatitis. Response to cortisone (E. C.).

adrenals adequately, possibly because of suppression of adrenal activity by the previous long-continued cortisone.

CASE 7

Vernal catarrah. (Case 7.) R. R., aged 10 years, a white schoolboy, had the chief complaint of conjunctivitis, both eyes, of four years' duration.

Past history. This patient developed a bilateral conjunctivitis with itching, burning, and tearing in 1946. A diagnosis of vernal catarrh was made. Since that time the conjunctivitis had become progressively worse and failed to respond to any treatment.

Large papillas developed in the palpebral conjunctiva of the upper and lower lids. Five radium treatments were given to the conjunctiva in 1947 without effect. A number of the large papillas were excised in 1948, followed by application of CO_2 snow. They promptly recurred. Antihistaminics, local chemicals, and antibiotics failed to relieve the condition. A change to a cold climate also caused no alleviation of his symptoms.

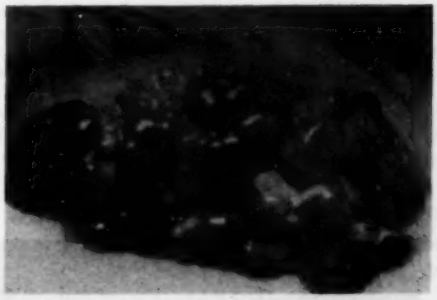

Fig. 13 (Hogan, *et al.*). Case 7. Vernal catarrh, right eye, prior to treatment.

Present history. The conjunctivitis, photophobia, lacrimation, and blepharospasm persisted and caused such disability that he could not attend school. He was referred to one of us (P. T.) by Dr. Edward J. Simons of Beverly Hills, California, to whom we are grateful for permission to publish these findings.

Examination showed a severe palpebral vernal catarrh with involvement of the upper and lower conjunctivas by firm large polypoid papillas (fig. 13). There was an abundant thick stringy mucoid secretion in the cul-de-sacs. Cultures showed numerous pathogenic staphylococci and scrapings showed polymorphonuclear leukocytes and eosinophils with many eosinophilic granules.

Slitlamp microscope examination showed a characteristic epithelial keratitis in both eyes.

He was admitted to the hospital on April 4, 1950, for treatment with cortisone. Treatment was started on April 8th. The dosage and results in both eyes are given in Chart 11.

Course. The conjunctival signs started to disappear on the fourth day and there was dramatic

Pt: R.R.

DATE	CORTISONE MG.	CONJUNCTIVITIS	KERATITIS	SIZE OF PAPILLAE	CONJUNCTIVAL EOSINOPHILES	PATHOGENIC STAPH
Apr. 8	200	4+	4+	4+	4+	4+
9	200	4+	4+	4+	4+	4+
10	100	4+	3+	4+	3+	3+
11	100	3+	3+	4+	3+	3+
12	100	3+	1+	4+	2+	2+
13	100	2+	0	3+	1+	1+
14	100	2+	0	3+	0	0
15	100	2+	0	3+	0	0
16	100	2+	0	3+	0	0
17	100	2+	0	3+	0	0
18	100	2+	0	3+	0	0
19	100	2+	0	2+	0	0
20	100	1+	0	3+	0	0
21	50	1+	0	2+	0	0
22	50	1+	0	1+	0	0
23	25	1+	0	1+	0	0
24	25	1+	0	1+	0	0

Chart 11 (Hogan, *et al.*). Vernal catarrh. Response to cortisone (R. R.).

clearing of the corneas. By the sixth day he had no subjective symptoms, the conjunctivas were pale and the corneas did not stain. Between the 9th and 14th days the papillas decreased in size rapidly, but never completely disappeared (fig. 14).

Toward the end of treatment some of the signs of Cushing's syndrome appeared with rounding of the face and abdominal distention. There was no hypertension.

In a subsequent letter Dr. Simons stated that all of the signs of vernal catarrh recurred three weeks after cessation of cortisone.

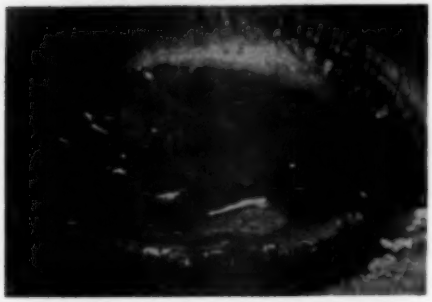

Fig. 14 (Hogan, *et al.*). Case 7. Vernal catarrh. Improvement after 14 days of treatment (right eye).

Comment. This patient responded rapidly to cortisone treatment, and within six days was entirely comfortable. A complete subsidence of the conjunctival papillas did not occur after 16 days, but it was necessary to discontinue treatment because of the signs of early Cushing's syndrome.

Discussion

Case 1

Chronic bilateral rheumatoid uveitis. The ocular condition responded partially to ACTH in that the signs of iridocyclitis almost, but not completely, disappeared. With subsidence of the iridocyclitis, however, the ocular tension rose, and could not be controlled.

An iridectomy in the left eye during treatment was not followed by any interference with normal healing despite continued administration of ACTH. Previous reports in the literature have indicated that the administration of ACTH might interfere with the healing of wounds because of its deterrent effect on the formation of granulation tissue. Therefore we were gratified to note that convalescence was uneventful in this case.

Laboratory evidence of decreasing adrenal cortical response to ACTH coincident with failure of improvement of the arthritis and uveitis caused us to discontinue treatment. This was followed by an immediate intensification of the uveitis, and coincident decrease of ocular tension to low levels. The partial failure of ACTH in this case might be explained as due to a failure of the adrenals to respond adequately.

Cortisone was given at a later date and the response was good, in that there was definite improvement in the arthritis, a fairly complete remission of the uveitis in the left eye, but almost no change in the right eye. These differences are difficult to explain.

Coincident with improvement of the uveitis in the left eye the ocular tension again rose. A cyclodialysis failed to lower the pressure. Inasmuch as treatment was unassociated with elevation of pressure in any of the other cases of this series we are more inclined to attribute the rise as due to subsidence of the iridocyclitis.

This patient has obtained, during a period of six months' treatment with ACTH and cortisone, partial improvement of his joint manifestations, so that he is able to get around on crutches, but has received very little benefit from an ocular standpoint.

Case 2

Acute rheumatoid uveitis. This patient obtained fairly rapid relief with cortisone. The eye and joint manifestations responded quickly to what is considered a very adequate dose of cortisone, but after 18 days' treatment the eyes still showed some signs of activity.

The acute iridocyclitis recurred shortly after withdrawal of cortisone and gradually subsided over a period of two and one-half months. Of particular interest was the activation of a subacute iridocyclitis in the previously unaffected left eye after withdrawal of treatment.

The implications of this response are important and must be considered in the treatment of patients with one normal and one diseased eye, or in patients with only one eye. It is probable the treatment should have been continued over a longer period in this case.

CASE 3

Acute rheumatoid uveitis. This patient obtained an adequate clinical and laboratory response to ACTH, but the iridocyclitis in the right eye never completely cleared. The acute inflammation recurred in both eyes within one week after stopping treatment. During a second course of treatment 40 mg. ACTH produced only moderate improvement. A different batch of ACTH, given in a dose of 60 mg. daily, later produced more marked improvement, but at the end of one week a one-plus flare and cells were present in the aqueous of both eyes.

The patient obtained only partial relief by this method of treatment, and a complete subsidence of the iridocyclitis has never been attained.

The results in these three cases of rheumatoid uveitis treated with ACTH and cortisone indicate that the acute phase of the inflammatory reaction may subside, leaving a residual low-grade inflammation which persists in spite of further treatment. It is possible that with a larger dosage or prolonged treatment a more complete response might be obtained. Too many conclusions cannot be drawn from so few cases.

CASE 4

Chronic recurrent granulomatous uveitis with secondary glaucoma. This case is the only one in this group which completely responded to treatment, and remained in a state of remission for two months with subsequent asymptomatic relapse. At the onset the iridocyclitis was mild. Treatment did not aggravate the already existent glaucoma. It is interesting that this granulomatous process responded to cortisone.

CASE 5

Acute bilateral uveitis and papillitis. This patient responded rapidly and completely to cortisone so that, except for a few vitreous opacities and slight evidence of a papillitis in the left eye at the end of 18 days, she appeared entirely well. Three days after discontinuing cortisone this eye again developed an acute episode and since that time there have been recurrent acute attacks in both eyes. Cortisone may be said to have terminated one acute attack but did not induce a permanent state of remission.

CASE 6

Atopic dermatitis and keratoconjunctivitis. This patient presented a desirable case to treat, for he had never achieved relief by any method of treatment. The improvement in the dermatitis and keratoconjunctivitis within five days after starting cortisone and their almost complete disappearance in three weeks provided great satisfaction. The conjunctival eosinophils disappeared in three weeks, but pathogenic staphylococci persisted. It had been impossible to rid the conjunctiva of organisms prior to treatment, but with bacitracin and chloromycetin they now promptly disappeared.

A relapse occurred promptly after withdrawal of cortisone. At a later date his adrenal cortices failed to respond to ACTH on two different occasions. A second course of cortisone produced a slower response, but eventually a satifactory one. The clinical failure with ACTH presumably reflects the inability to stimulate the adrenals properly, possibly from inadequate dosage.

CASE 7

Vernal catarrh. The prompt response to cortisone was dramatic, and the relapse following its discontinuance discouraging. However, in a case as severe as this, any medication which brings relief, even though temporary, offers hope that a more permanent cure will follow.

Summary and Conclusions

1. One case of bilateral chronic rheumatoid uveitis was treated with both ACTH and cortisone. A fair response in the joints resulted so that the patient was able to walk on crutches, but the eyes, after six months' treatment, are unimproved. Two surgical procedures were performed on the left eye for glaucoma during treatment without complication or interference with wound healing.

2. One case of unilateral acute rheumatoid uveitis was treated with cortisone, and responded rapidly, but after 18 days a slight residual inflammation persisted. After treatment was stopped the inflammation again became acute, and, in addition, an inflammation developed in the opposite eye. This response in the opposite eye may be important in the future selection of cases for treatment.

3. Another case of bilateral acute rheumatoid uveitis was treated with ACTH. The acute phase of the inflammation subsided promptly, but a slight chronic inflammation persisted in spite of an adequate adrenal response. The process in both eyes again became acute after withdrawal of ACTH. Reinstitution of treatment caused only moderate improvement, and a poor adrenal response. A change to a different batch of ACTH and an increase in the dosage resulted in a good adrenal response and marked, but not complete, subsidence of the uveitis up to the date of this report.

4. One case of acute bilateral nongranulomatous uveitis and papillitis was treated with cortisone and healed rapidly, except for slight residual inflammation in the left eye. The inflammation recurred three days after cessation of treatment.

5. One case of atopic dermatitis and atopic keratoconjunctivitis showed dramatic improvement with cortisone after one month but the lesions recurred after treatment was stopped on the 64th day. Subsequent trial on ACTH on two occasions failed to stimulate the adrenal cortices properly, possibly due to inadequate dosage, an impotent batch, or both. A second course of cortisone later caused a more gradual but satisfactory response.

6. One case of severe vernal catarrh responded rapidly to cortisone so that the patient was completely comfortable in three weeks. The condition promptly relapsed after cessation of treatment.

7. Only two patients developed any physiologic alterations as a result of this treatment. Case 6 developed a mild hypertension, slight acne, and facial signs of Cushing's syndrome after five weeks' treatment with cortisone. These signs subsided after treatment was discontinued. Case 7 also developed the facial contour and abdominal distention of Cushing's syndrome after three weeks' treatment.

450 Sutter Street (8).

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RELATION OF STEROID HORMONES TO THE DEVELOPMENT OF EXPERIMENTAL EXOPHTHALMOS*

GEORGE K. SMELSER, PH.D., AND V. OZANICS, M.S.
New York

It has always been accepted that the two sexes are not affected with equal frequency or severity by thyrotoxicosis or exophthalmos. Whereas, such ratios as four females to one male are quoted in the incidence of exophthalmic goiter, the occurrence of severe exophthalmos, especially of the postthyroidectomy type, has been found greater in men (Marine,[1] Oppenheimer,[2] Means[3]). Such statistics strongly suggest some relation of the sex steroid hormones to exophthalmos.

In addition, the clinical reports (Brain and Mann,[4] Halpern[5]) on the occasional use of sex hormones in the treatment of exophthalmos, and the experimental studies of Marine, stimulated us to evaluate the effect of some of the steroid hormones of the gonads and adrenal glands on the experimental exophthalmos produced by pituitary extracts, which simulates clinical exophthalmos.

One hundred and 54 guinea pigs of both sexes were used in these studies. All were thyroidectomized when they attained 270 to 290 gm. of body weight. Exophthalmos was produced by injection of pituitary extracts subsequent to thyroidectomy, as reported in previous articles (Smelser[6,7]).

In some experiments it was desired to determine if absence of the gonads played any role in the development or degree of exophthalmos to be produced. In these cases both sexes were gonadectomized at approximately weaning age (190 to 220 gm. in weight) long before thyroidectomy was performed.

A portion of both the spayed female and the castrated male guinea pigs were reserved as control animals and the others were injected with anterior pituitary extract for 15 to 34 days. Paired experimental and control animals always received indentical treatment.

The same pituitary extract was administered to intact male and female animals and to castrated male guinea pigs which received testosterone propionate parenterally. The effect of the pituitary extracts on the orbital contents and the production of exophthalmos in these groups was compared as will be described.

In addition to these deficiency experiments, others were done in which an excess of the steroid hormone was administered to intact and gonadectomized animals.

The effect of the following hormone preparations on experimental exophthalmos was determined: Androgen (testosterone propionate,[1] 5.0 mg. per day); estrogen (α-estradiol dipropionate, 0.025 mg. per day); adrenal cortical hormones (11-desoxycorticosterone acetate,[1] 5.0 mg. per day); cortical extract, Upjohn (6.5 to 15 rat units per day); and cortisone acetate (5.0 mg. per day). Adrenocorticotrophic hormone (ACTH),[2] although not a steroid, was used to stimulate the endogenous production of adrenal hormones. Twelve and one-half mg. of a freshly made saline suspension were injected twice daily.

The effect of the steroid hormones on exophthalmos was determined in paired experiments. Exophthalmos was produced in a group of guinea pigs and, as soon as the proptosis was definite, pairs of these were selected in which the exophthalmos appeared to be equally developed.

One of each pair of these animals was then injected daily with the hormone to be tested for a period of 10 days. At that time the degree of exophthalmos was estimated by comparison with the paired control animal which had received the same pituitary extract, but no other treatment, and the animals were autopsied.

* From the College of Physicians and Surgeons, Columbia University.

The degree of exophthalmos was measured postmortem, the orbital contents weighed, and the tissues fixed in Bouin's fluid for histologic study. Paraffin sections were cut at 6μ and stained in Masson's trichromic stain.

Results

Androgen series

Neither the lack nor excess of androgen had any marked effect on the orbital structures or the protrusion of the eyes of thyroidectomized guinea pigs. The data, a portion of which is summarized in Table 1, based on 19 cases, do not show any significant differences between those animals receiving an excess of androgen and the castrates which were deficient in this hormone. The slight difference of 0.3 mm. in the protrusion of the globe between the castrate and hyperandrogen group may be regarded as insignificant.

That a marked difference in the androgen level was attained in these animals was demonstrated by the difference in weight of the accessory reproductive organs. The accessory organ weight of the castrates was 910 mg., whereas that of the androgen-treated averaged nearly 5,000 mg. The accessory organs of the intact males weighed 3,700 mg.

The effect of androgens on experimentally produced exophthalmos was tested in several series of experiments. The first of these consisted of seven castrate male animals in which exophthalmos had been produced by a series of injections of a single preparation of pituitary extract. The guinea pigs were then separated into two groups in which the exophthalmos was judged to be equally developed and testosterone was administered daily to one group for approximately 10 days. These groups were very small, but good exophthalmos was maintained in both. The degree of exophthalmos as judged by the protrusion of the globe postmortem was equal. The orbital fat averaged much heavier in the testosterone treated cases, but this was due to the inclusion of two unusually swollen orbits.

In the second experiment seven male and 10 castrate male animals were injected with equal amounts of a single pituitary preparation. When exophthalmos was evident in the intact male group, injections of testosterone were initiated, so that during the 10 days prior to autopsy an excess of androgen was present. The exophthalmos of these animals was compared with that produced in the control castrate group. The exophthalmos produced was equal in both groups.

In the third set (17 cases), testosterone

TABLE 1

Effect of androgen* on orbital tissues and the protrusion of the eye of control and exophthalmic guinea pigs

Type and Treatment	No. of Cases	Protrusion† of the Eye (mm.)	Orbital Fat (mg.)	Extra-ocular Muscles (mg.)	Globe (mg.)	Body (gm.)
Control Series: Thyroidectomized, no pituitary extract injected.						
Male and androgen	4	3.4	33.7	79	434	413
Male	8	3.3	40.3	77	445	427
Castrate male	7	3.1	42.9	70	457	421
Exophthalmic Series: Thyroidectomized, injected with pituitary extract 20 mg/day.						
Male and androgen	8	3.8	49.7	87	438	422
Male	5	4.0	53.0	87	441	410
Castrate male	13	3.9	54.9	72	413	344

* Androgen = Testosterone propionate 5.0 mg./day for 29 to 33 days.
† Protrusion of the eye = distance from supraorbital notch to limbus measured postmortem after lids and skin are removed.

administration was initiated just prior to the first injections of pituitary extract so that the exophthalmos developed in the presence of a high concentration of androgen. This series may be compared with the castrate group in which exophthalmos was developed entirely in the absence of testicular secretion.

The controls to these two groups were normal male animals in which an exophthalmos had been produced. The exophthalmos was produced in all three groups by injections of the same preparation of the pituitary extract and was quite identical, yet the testicular hormone level was far greater in the androgen-treated group than in the others, as indicated by the weight of the accessory reproductive glands. The weight of the accessory reproductive glands of the castrate group averaged about 1.0 gm., whereas that of the androgen-treated males was over 7.5 gm.

Histologic preparations of the orbital fat tissues of these animals were made and studied. Marked edematous infiltration of the fat and loose connnective tissue which has been described was found in all groups, whether deficient in testicular hormone or treated with an excess of androgen. The appearance of the orbital fat in a control and an exophthalmic animal is shown in Figures 1 and 2. The level of androgenic hormone, therefore, appears to have no effect on the protrusion of the globe or on the orbital contents of normal or exophthalmic guinea pigs.

Estrogens

Six intact female animals were injected with 0.025 mg. α estradiol dipropionate daily for 10 days and at autopsy the protrusion of the eyes was measured and the orbital contents weighed. These data were compared with similar findings in a group of five normal and nine spayed female animals autopsied at this time. The spayed guinea pigs had been ovariectomized when of 190 to 220 gm. of body weight. The weights of the globes were very nearly the same though, due to the effect of the injected estrogen, the body weight of that group was less than that of the other two groups (table 2).

TABLE 2

Effect of estrogen* on orbital tissues and the protrusion of the eye of control and exophthalmic guinea pigs

Type and Treatment	No. of Cases	Protrusion of the Eye (mm.)	Orbital Fat (mg.)	Extra-ocular Muscles (mg.)	Globe (mg.)	Body (gm.)
Control series: Thyroidectomized, no pituitary extract injected.						
Female and estrogen	5	3.0	28.5	73	434	354
Female	6	3.5	47.1	76	444	424
Spayed female	9	3.6	45.9	76	441	378
Exophthalmic Series: Thyroidectomized, injected with pituitary extract 25–35 mg./day.						
Spayed female and estrogen	11	3.3	42.2	73	408	355
Spayed female	9	4.1	66.5	74	419	338

* Estrogen = α estradiol diproprionate 0.025 mg./day.

Estrogenic hormone in the amounts given apparently causes the eye to be more sunken in the orbit, probably by virtue of its effect on the orbital contents. The orbital fat of the estradiol-treated series was reduced in amount by 39 percent.

The extraocular muscles were not apparently affected, but the Harderian gland was definitely reduced in size. This reduction was greater in proportion than that of the body as a whole. Deficiency of estrogenic hormone had no obvious effect on the orbit, for the positions of the globe and orbital contents were quite normal in the spayed group.

Twenty gonadectomized female guinea

pigs were injected daily with the same preparation of pituitary extract. When exophthalmos developed, pairs were selected in which the ocular protrusion appeared to be equal and one animal of each pair was given a daily injection of 0.025 mg. of α estradiol dipropionate and the pituitary extract injections were continued as before. The estradiol was injected for 10 days, when both animals were autopsied. The data so obtained are shown in Table 2.

Injection of estrogenic hormone appears definitely to reduce the exophthalmos experimentally produced and the hypertrophy of the orbital fat and Harderian gland which is its cause. This result not only appeared in the averaged data, but was quite consistent, since there was only one instance in the 11 cases studied when this result was not obtained.

Estrogen treatment markedly altered the histologic appearance of the orbital fat. The large quantities of stainable edematous infiltrate usually seen following the pituitary extract injections were either absent or markedly reduced, as shown by comparison of Figures 2 and 4. In most of the cases marked proliferation of fibrous tissue had taken place, so that the entire character of the orbital fat was changed (fig. 3).

This modification of the orbital fat was also occasionally found in those animals which received estrogen but no pituitary extract; therefore, the reaction appears to be one induced by the steroid, rather than a result of the interaction of the pituitary and estrogenic hormone.

The section of orbital fat shown in Figure 5 is one in which the fibrosis occurred. The number of fat cells seemed to be reduced in this group, but this observation is not based on any quantitative measurement. The mass of fibrous tissue contained many cells, probably fibroblasts.

The histologic appearance agreed well with the gross appearance seen at autopsy, when it was observed that the orbital fat of estrogen-treated animals, both pituitary treated and control, was tough, dry, and opaque. Ordinarily the orbital fat of exophthalmic animals is gelatinous, moist, and translucent.

Adrenal series

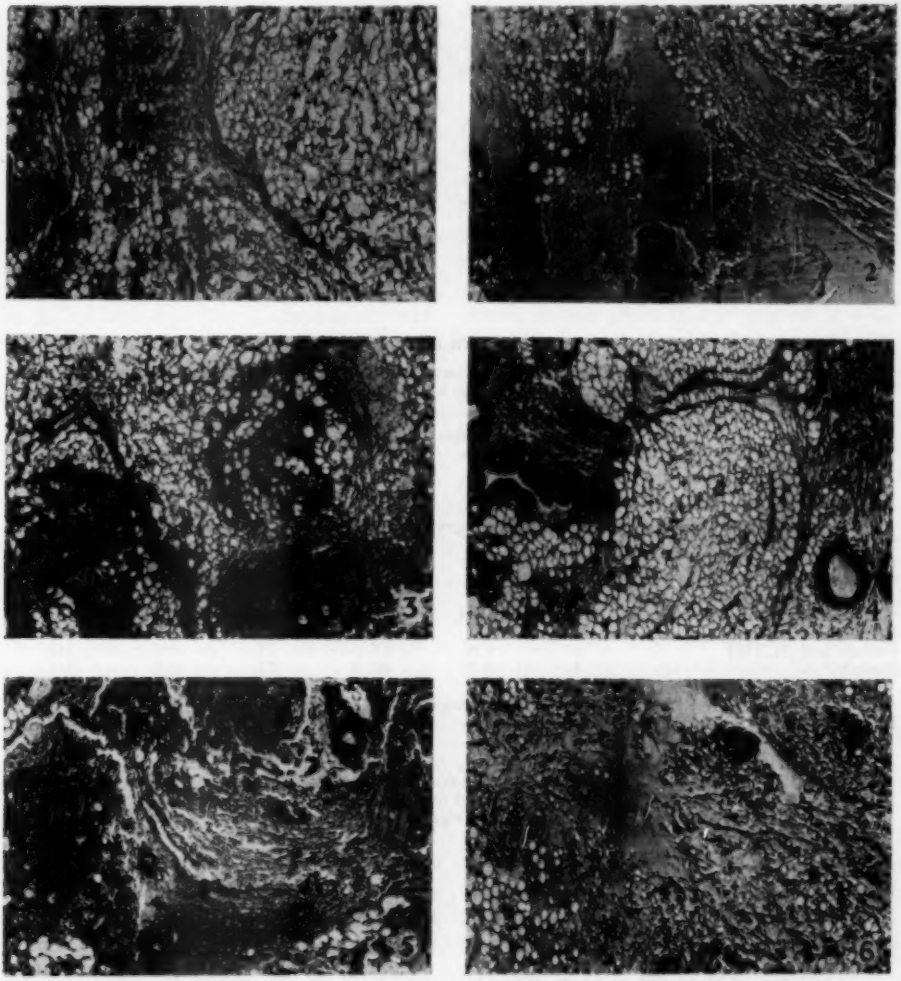
The effect of several adrenal hormone preparations on experimental exophthalmos was tested. Exophthalmos was produced in the usual manner and, as soon as a definite proptosis was noted, pairs of animals with equally developed exophthalmos were selected, as in the estrogen series. One of each pair was treated with the hormone to be tested, and the pituitary extract injections were continued in both animals until autopsy 10 days later. Two series of experiments were made.

In the first, either desoxycorticosterone or adrenal extract (Upjohn) was given. The same preparation of pituitary extract was used for both control animals and the adrenal treated series. In the second series of experiments cortisone and adrenocorticotrophic hormone (ACTH) were tested. A second group of control animals was provided for this series.

Normal and spayed female animals as well as castrate males were used in these experiments, in order to check the possibility that some steroid product of the gonads might influence the results. The control and adrenal hormone group both contained normal and gonadectomized animals.

Results of the treatment with all four hormone preparations may be considered together. None of the preparations used had any effect on exophthalmos. There was no reduction in the proptosis in any group and the orbital tissues were unaffected in weight. The exophthalmos was not only unaffected by the hormone treatment as judged by the average values given in Table 3, but the data were consistent; that is, the exophthalmos was maintained in all but three cases of the 23 guinea pigs treated, and in the control group the exophthalmos also continued in all but two of the 21 animals.

Unlike estradiol, the adrenal cortical hor-



Figs. 1 to 6 (Smelser and Ozanics). (1) Section of orbital fat of a thyroidectomized, uninjected, non-exophthalmic guinea pig.

(2) Section of orbital fat of an exophthalmic guinea pig.

(3) Section of orbital fat of an exophthalmic guinea pig which had been treated with estradiol for the 10 days prior to autopsy. Note the marked increase in connective-tissue fibers and the reduction of edematous infiltrate.

(4) Section of orbital fat of another estradiol-treated exophthalmic guinea pig in which the edema was markedly reduced but an increase in fibrous tissue was not found.

(5) Section of orbital fat of a thyroidectomized, estradiol-treated animal. No pituitary extract had been given.

(6) Section of orbital fat of an exophthalmic guinea pig which had been treated with 5.0 mg. cortisone per day for the 10 days prior to autopsy. The edema is marked, typical of the orbital fat of a good case of experimental exophthalmos.

mones and ACTH had no effect on the histologic structure of the orbital fat. This tissue was highly edematous in the treated as well as in the control exophthalmic animals. The excessive amount of fibrous tissue found in the estrogenic series was not noted in the adrenal group. Figure 6 shows a section of the orbital fat of a cortisone-treated exophthalmic guinea pig.

Seven animals, which had not received pituitary extract, were injected with either cortisone or ACTH to determine if these hormones alone had any effect on the orbital structures. The same dosage of cortisone was used as in the other experiments, but the ACTH dosage was varied from 25 mg. per day to 50 mg. per day. The injections were continued for 10 days, at which time the animals were killed. These treatments had no effect on the position of the globe or on the weight of the orbital tissues.

TABLE 3

EFFECT OF ADRENAL HORMONES ON ORBITAL TISSUES AND THE PROTRUSION OF THE EYE OF CONTROL AND EXOPHTHALMIC GUINEA PIGS

Type and Treatment	No. of Cases	Protrusion of the Eye (mm.)	Orbital Fat (mg.)	Extra-ocular Muscles (mg.)	Globe (mg.)	Body (gm.)
Exophthalmic Series: Thyroidectomized, injected with pituitary extract 25–30 mg./day.						
Spayed female and DOCA*	6	4.2	62.1	75	429	349
Spayed female	8	4.3	74.3	77	401	322
Gonadectomized males & females & cortical extract†	6	4.3	73.8	83	404	358
Gonadectomized males & females	5	4.14	70.9	83	404	337
Female and cortisone‡	5	4.1	58.5	85	401	368
Female and ACTH§	6	4.0	53.0	75	416	315
Female	8	4.2	67.0	78	392	346
Control: Thyroidectomized, no injections						
Female	4	2.9	32.8	67	422	382

* DOCA = 11-desoxycorticosterone acetate, 5.0 mg./day for 10 days.
† Cortical Extract = 6.25 to 15 rat units/day, Upjohn.
‡ Cortisone = cortisone acetate, 5.0 mg./day for 10 days.
§ ACTH = adrenocorticotrophic hormone 5.0 mg. equivalent to 1.0 mg. hormone per day, for 10 days.

Discussion

In experiments such as those just reported, the effect of the steroid hormones on experimentally induced exophthalmos could be exerted on either the reacting tissues themselves—for example, on the orbital fat—or on the mechanism by means of which the pituitary extract produces the edematous swelling. The amount of pituitary hormone supplied by injection of the extract was relatively constant and not at all affected by the steroids studied.

If such experiments had been done in cases where exophthalmos was caused by some endogenously produced hormone, as may be the case in clinical exophthalmos, the amount of exophthalmos-causing hormones secreted might be affected with results to the exophthalmos entirely different from those described here.

Several of the steroid hormones studied in these experiments are known to inhibit the secretion of certain hypophyseal hormones, but whether they affect the rate of production of the exophthalmos-producing factor(s) is not shown by the present study.

A few reports may be found in the literature in which the use of steroid sex hormones was found to affect clinical exophthalmos favorably (Brain and Mann[4]). A number of laboratories have studied the effect of sex hormones experimentally and

found that exophthalmos was not affected by the sex of the experimental animal, or gonadectomy (Smelser,[7] Dobyns[8]).

Marine and Rosen (1936,[9] 1938[10, 11]), however, in a study of exophthalmos, mainly in rabbits, which had been produced by the injection of methyl cyanide, found that this type of exophthalmos was prevented by gonadectomy in both male and female animals, and that castration caused established exophthalmos to regress in three instances. In the converse experiment, administration of testosterone increased preëxisting exophthalmos or produced it in thyroid-deficient animals which had shown a tendency toward exophthalmos. Injections of esterone 200 R.U. per day did not affect exophthalmos in these cases.[9]

These results are difficult to correlate with those reported here except on the basis that the exophthalmos produced by cyanide in rabbits is different from that caused by pituitary extracts in guinea pigs. The mechanism in the latter is not dependent on the sympathetic nervous system; whereas, cyanide exophthalmos in the rabbit apparently is.

In the experiments described here neither excess nor deficiency of androgens affected exophthalmos. The adrenal cortical hormones likewise did not affect the exophthalmos. It was thought that, in view of the influence some adrenal hormones exert on water balance, the accumulation of fluid in the orbit might be modified. Cortisone was employed in these experiments because of its effect on the proliferation and function of connective-tissue elements. These two phases of adrenal-steroid function do not appear to be involved in experimental exophthalmos of this type.

In those experiments in which ACTH was given alone no effect was noted in the orbital tissues, yet the hormone preparation was quite active as shown by the very large adrenal glands which were found at autopsy. It would appear, therefore, that ACTH is not the factor in the crude pituitary extracts which is responsible for the production of exophthalmos. Jefferies[12] reports that two daily injections of ACTH into intact guinea pigs did not produce an exophthalmos.

The effect of estradiol on the orbits of control and exophthalmic guinea pigs was surprising in view of the quite opposite effect estradiol has on the water content of some tissue, such as the sex skin of the monkey or the uterus of rats. However, the specificity of action of estrogens, as shown in growth stimulation of some smooth muscle and not others, is very great. It is of interest to note that, although the exophthalmos was less in the estrogen-treated animals than in control animals, the tissues did react to the pituitary extract.

If the degree of protrusion of the globe and the weight of orbital fat of estrogen and pituitary-extract treated animals are compared with that of guinea pigs which received estrogen only (table 2), it will be seen that the pituitary treatment produced a definite effect. A similar relationship exists with thyroxin (Smelser[13]) which, like estradiol, affects the orbital tissues directly, decreasing their mass, but does not prevent them from reacting to injected pituitary hormone.

Two explanations of the sex ratio of the incidence of exophthalmos, especially that of the postthyroidectomy type, suggest themselves. If clinical exophthalmos of this sort is caused by a hypersecretion of some pituitary principle, it may be that the male hypophysis elaborates and releases this substance in greater quantity than does the female. Such a function may or may not be influenced by the sex or adrenal steroids, and the present experiments shed no light on this possibility.

If, however, such an hypothetic substance is released equally by the pituitary glands of both sexes, it would, according to the present experiments, be less effective in the presence of estrogens and, therefore, relatively more active in males. At menopause, when the estrogen level would decrease in women, this relation would not hold. Oppenheimer[2]

comments on the increase in the frequency of the occurrence of exophthalmos in women of that age group. The possibility is an interesting one, if hypothetic.

Summary

1. Experimental exophthalmos of the type discussed here is not affected by the absence of the gonads or by an excess of androgens (testosterone) administered parenterally.

2. Gonadectomy, or testosterone administration, does not affect the protrusion of the eye or the mass of orbital tissue in the guinea pig.

3. Injection of adrenal cortical hormones (adrenal cortical extract, desoxycorticosterone, and cortisone) had no effect on the orbital tissue of control and exophthalmic animals and did not influence the degree or incidence of exophthalmos in these experiments.

4. Adrenal cortical hormones secreted endogenously under the influence of ACTH stimulation also were without effect on the exophthalmos which had been produced.

5. Although gonadectomy in the female did not apparently influence exophthalmos, administration of large amounts of estradiol did reduce the exophthalmos in 10 of 11 cases. The weight and histologic structure of the orbital fat was definitely changed, and in some cases a marked fibrosis of this tissue was found.

6. Similar effect was occasionally evoked when estradiol was administered to control, nonexophthalmic, thyroidectomized guinea pigs.

7. Explanations of the sex ratio in the incidence of clinical exophthalmos are discussed.

630 West 168th Street (32).

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STUDY ON PENETRATION OF CYSTEINE AND CYSTINE INTO THE AQUEOUS HUMOR OF RABBITS AND ITS RELATION TO EARLY X-IRRADIATION EFFECTS ON THE EYE*

LUDWIG VON SALLMANN, M.D., ZACHARIAS DISCHE, M.D., GABRIELE EHRLICH, PH.D., AND CARMEN M. MUNOZ, B.A.
New York

In the last year, two experimental studies dealt with the protection of mice and rats against X-irradiation by chemical compounds which were administered parenterally.

Z. M. Bacq and co-workers[1,2] reported an increase in the survival rate of mice up to 80 percent when 0.1 mg. of sodium cyanide was injected before exposure of the animals to a lethal dose of X rays (500 to 600 r, 230 K.V., 12 ma., filter 0.25 mm. Cu, TSD 50 cm., field 100 sq.cm., r/min. 30).

H. M. Patt and co-workers[3] injected intravenously into rats a 20-percent solution of cysteine in doses from 175 to 875 mg./Kg. shortly before or shortly after total body irradiation with 800 r (250 K.V., 15 ma., filter 0.5 mm. Cu, and 3.0 mm. bakelite, TSD 27.5 cm., r/min. 210).

About 82 percent of the animals pretreated with cysteine survived. Of the animals treated with cysteine after exposure to X rays and of those controls which received sodium-chloride solution or cystine, about 19 percent did not succumb to irradiation injury.

In the present study X-ray effects were examined in the eyes of rabbits which were pretreated with cysteine. Preliminary experiments were also carried out to evaluate the protective influence of local treatment of the eye with sodium cyanide against X-ray injuries to the crystalline lens.

From the experimental results reported by Patt and co-workers, it seemed desirable to obtain relatively high levels of cysteine in the tissues as a possible preventive against X-ray damage. Since, to the best of our knowledge, there have been no reports on the penetration of cysteine and cystine into the eye after local or systemic administration, it was necessary to determine the passage of these amino acids into the aqueous humor from the blood or after local application. These determinations provided the first part of the study.

CYSTINE-CYSTEINE RATIO

(The appearance and disappearance curves of these amino acids in blood and aqueous humor after systemic and local administration.)

TECHNIQUE

A 16-percent solution of L-cysteine (free base) was injected intravenously in a dose of two gm. per rabbit (700 to 800 mg./Kg.). A four-percent solution served for intraperitoneal injection but only one gm. in 25 cc. of water could be given to the individual animals. An aqueous solution containing four-percent cysteine base is isotonic to a 0.9-percent solution of sodium chloride.

One cc. of an eight-percent solution of cysteine was administered subconjunctivally and the same concentration was used for iontophoretic introduction from the negative pole (2.0 ma., 5.0 min.). One gm./Kg. of neutralized cysteine hydrochloride and the same amount of L-cystine in aqueous suspension were fed to experimental animals by stomach tube. The content of the amino acids was measured in whole blood or in plasma and in aqueous humor.

The following procedures were used: 0.4 cc. of whole blood was mixed with 5.6 cc.

* From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and the Institute of Ophthalmology, Presbyterian Hospital. This study is a part of the work performed under Contract #AT-30-Gen-70 of the Atomic Energy Commission.

This study was also supported by the Knapp Memorial Foundation.

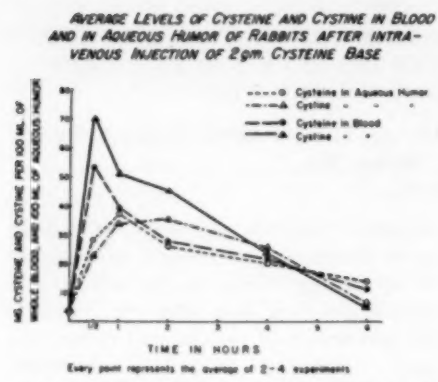

AVERAGE LEVELS OF CYSTEINE AND CYSTINE IN BLOOD AND IN AQUEOUS HUMOR OF RABBITS AFTER INTRAVENOUS INJECTION OF 2 gm. CYSTEINE BASE
Cysteine in Aqueous Humor
Cystine
Cysteine in Blood
Cystine
MG. CYSTEINE AND CYSTINE PER 100 ML. OF WHOLE BLOOD, AND PER 100 ML. OF AQUEOUS HUMOR
TIME IN HOURS
Every point represents the average of 2-4 experiments

Fig. 1 (von Sallmann, Dische, Ehrlich, and Munoz). Blood and aqueous levels of cysteine and cystine.

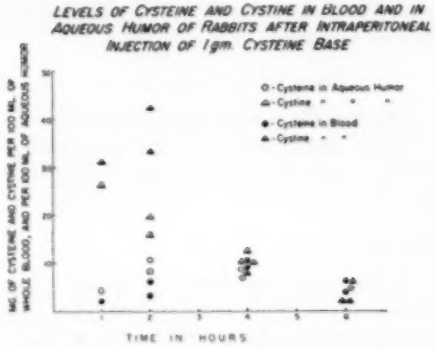

LEVELS OF CYSTEINE AND CYSTINE IN BLOOD AND IN AQUEOUS HUMOR OF RABBITS AFTER INTRAPERITONEAL INJECTION OF 1 gm. CYSTEINE BASE
O - Cysteine in Aqueous Humor
Δ - Cystine
● - Cysteine in Blood
▲ - Cystine
MG. OF CYSTEINE AND CYSTINE PER 100 ML. OF WHOLE BLOOD, AND PER 100 ML. OF AQUEOUS HUMOR
TIME IN HOURS

Fig. 2 (von Sallmann, Dische, Ehrlich, and Munoz). Blood and aqueous levels of cysteine and cystine.

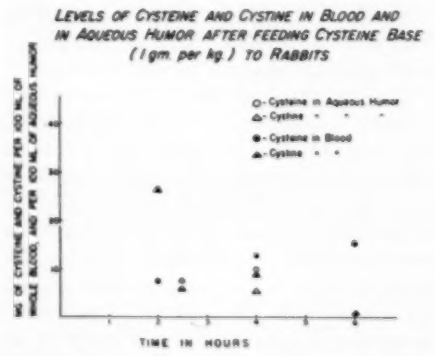

LEVELS OF CYSTEINE AND CYSTINE IN BLOOD AND IN AQUEOUS HUMOR AFTER FEEDING CYSTEINE BASE (1 gm. per kg.) TO RABBITS
O - Cysteine in Aqueous Humor
Δ - Cystine
● - Cysteine in Blood
▲ - Cystine
MG. OF CYSTEINE AND CYSTINE PER 100 ML. OF WHOLE BLOOD, AND PER 100 ML. OF AQUEOUS HUMOR
TIME IN HOURS

Fig. 3 (von Sallmann, Dische, Ehrlich, and Munoz). Blood and aqueous levels of cysteine and cystine.

of ice-cold 0.9-percent solution of sodium chloride. The plasma thus diluted was separated from the blood by high speed centrifugation at 0°C. and was treated with two cc. of a 16-percent solution of trichloracetic acid.

After the sample had been allowed to stand for two minutes and then centrifuged at high speed for three minutes, the deproteinized fraction was poured off and stored at low temperature until the analyses were made. The concentration of cysteine and cystine in plasma was calculated on the assumption that the amino acids do not enter the red cells. The quantities measured in diluted plasma were identical therefore with those determined in samples of whole blood taken for analysis.

Whole blood was handled in a similar way, but deproteinization with trichloracetic acid was carried out immediately before the samples were centrifuged. Although in plasma the initial values of –SH and –S–S– groups are negligible, in whole blood they are high. This is due to the content of reduced and oxydized glutathione in red cells. The blank values were subtracted from the readings obtained after injection of cysteine and in this way the concentration of cysteine or cystine was determined for whole blood.

A mixture of 0.2 cc. of aqueous humor with 2.8 cc. of cold saline and one cc. of 16-percent trichloracetic acid was made and then stored at low temperature as usual. Controls of aqueous humor and blood from untreated rabbits were run simultaneously in all instances.

In four in vitro experiments on oxidation of cysteine to cystine, 0.4 cc. of pooled aqueous was added to 0.2 cc. of a solution of L-cysteine base containing 100 mg. percent of the amino acid. The mixtures were allowed to stand at room temperature for 15 minutes, one or three hours, and were then deproteinized with a five-percent solution of trichloracetic acid.

The same technique was followed in the control experiments made with a 0.9-percent

solution of sodium chloride and with triple distilled water.

For determination of the sulfhydryl groups (–SH) and the disulfide bonds (–S–S–) the new spectrophotometric micro method of Z. Dische and H. Zil[4] was employed. Altogether 49 experiments were carried out in this part of the study.

Results and comment

Figures 1 to 6 indicate the concentrations of cysteine and cystine in samples of blood

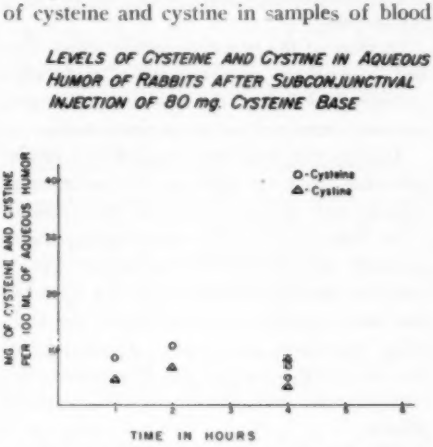

LEVELS OF CYSTEINE AND CYSTINE IN AQUEOUS HUMOR OF RABBITS AFTER SUBCONJUNCTIVAL INJECTION OF 80 mg. CYSTEINE BASE
MG OF CYSTEINE AND CYSTINE PER 100 ML. OF AQUEOUS HUMOR
O-Cysteine
Δ-Cystine
TIME IN HOURS

Fig. 4 (von Sallmann, Dische, Ehrlich, and Munoz). Aqueous levels of cysteine and cystine.

or plasma and of aqueous humor at stated intervals after administration by local or systemic routes.

The absolute amounts of the amino acids and the cysteine-cystine ratio in the body fluids examined were greatest after the intravenous injection of the cysteine base (fig. 1). The curves for cysteine in the aqueous reached their peaks (35 mg. percent) within one hour. Following this, there was a relatively steep decline which flattened out after one hour. The cysteine-cystine ratio which was slightly more than one at the one-hour interval, decreased at later periods except at the reading after six hours.

Intraperitoneal (fig. 2) and oral (fig. 3) administration resulted in lower concentration of the substances in the various samples when compared to the previous series, corrections having been made for difference in the administered doses of the amino acids.

Subconjunctival injections (see Figure 4) brought about a range of values in the aqueous humor similar to that measured

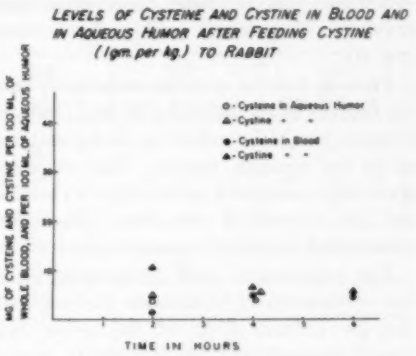

LEVELS OF CYSTEINE AND CYSTINE IN BLOOD AND IN AQUEOUS HUMOR AFTER FEEDING CYSTINE (1gm. per kg.) TO RABBIT
MG OF CYSTEINE AND CYSTINE PER 100 ML. OF WHOLE BLOOD, AND PER 100 ML. OF AQUEOUS HUMOR
O-Cysteine in Aqueous Humor
Δ-Cystine " "
●-Cysteine in Blood
▲-Cystine " "
TIME IN HOURS

Fig. 5 (von Sallmann, Dische, Ehrlich, and Munoz). Blood and aqueous levels of cysteine and cystine.

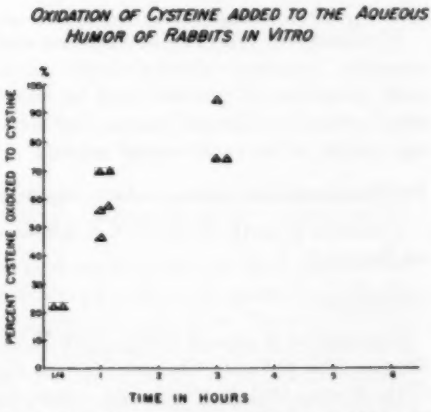

OXIDATION OF CYSTEINE ADDED TO THE AQUEOUS HUMOR OF RABBITS IN VITRO
PERCENT CYSTEINE OXIDIZED TO CYSTINE
%
TIME IN HOURS

Fig. 6 (von Sallmann, Dische, Ehrlich, and Munoz). Oxidation of cysteine.

after the intraperitoneal use but the cysteine-cystine ratio was more than one in contrast to the results after intraperitoneal injections.

The amounts in the aqueous humor after feeding cystine (fig. 5) or cysteine (fig. 3) were so small that they could not be considered accurate. The results of the experi-

ments with iontophoresis were not plotted because of the oxidation of cysteine during the iontophoretic procedure.

The experiment on the oxidation of cysteine to cystine in pooled aqueous humor in vitro showed that—at room temperature—cysteine was oxidized to a great part (average 77 percent) within three hours (fig. 6).

Thus in general cysteine underwent various degrees of oxidation on its way from the primary site of introduction of the material up to the aqueous humor. This oxidation apparently continued in the anterior chamber and also occurred in vitro when cysteine had been added to pooled aqueous humor.

The experiments with intravenous injection demonstrated that both the oxidized and the reduced form of the amino acid passed through the blood-aqueous barrier with ease.

The levels of cysteine in blood and aqueous humor were close to equilibrium two hours after injection.

It seemed that processes of oxidation and reduction occurred simultaneously since small quantities of cysteine could be measured in blood and aqueous humor after feeding cystine to the experimental animals.

Pretreatment of rabbits with cysteine

(Relation to early effects of X-irradiation on the eye.)

Technique

One dose of X rays of 1,500 r (220 K.V., 20 ma., filter 0.5 mm. Cu, and 1.0 mm. Al, TSD 30 cm., field 20 mm. round, r/min. in air 145) was used on each eye of 22 chinchilla rabbits.

Similar to the technique described in the previous study,[5] the rabbits under nembutal anesthesia were placed on the animal board in a way that right and left eyes could each be irradiated separately with the other shielded eye outside of the beam of rays. Great care was exercised to procure the same incidence of the X-ray beam to the target and to have the lid margin within the 20-mm. field. The proper position of the animal's head was controlled during irradiation.

The right eye was irradiated before cysteine was used and injection of cysteine followed immediately after exposure to a single dose. The left eye was exposed to the X rays 30 minutes after intravenous injection of two-gm. cysteine per animal, or subconjunctival injection (80 mg.) and four hours after intraperitoneal administration of one gm. per animal.

In view of the negative results which Patt and co-workers reported when they used cystine, the effect of the oxidized amino acid was not examined in the present study.

The electric field was applied in one experiment, with an eight-percent solution of cysteine base used at 2.0 ma. for five minutes.

In four preliminary experiments iontophoresis was also used to introduce cyanide into the anterior chamber after the right eye had been irradiated according to the technique described previously.[6] Irradiation of the left eye was carried out 30 minutes after iontophoretic introduction of the metabolic poison.

All animals were examined biomicroscopically and with the ophthalmoscope at weekly or biweekly intervals for varying lengths of time.

Results

The acute exposure to 1,500 r of penetrating X rays produced an increase for two days in the protein content of the aqueous humor and migration of many cells into the anterior chamber which often formed a dense layer on the surface of the lens in the upper half of the pupil. Injection of conjunctival vessels and marginal hyperemia of the lids accompanied the intraocular changes.

Pigment-containing cells began to proliferate from the upper limbus into the cornea, in the shape of aprons or irregularly branched patterns, about three weeks following irradiation and shortly after the corneal epithelium showed clinical signs of

radiation damage by roughening of the surface, minute defects, and grayness of a broad zone reaching from the limbus to about the middle of the cornea.

After about two weeks the lid margin was usually red and swollen and the conjunctiva inflamed. Epilation set in at this time and progressed in the following weeks until it underneath the anterior capsule of the lens. The stage of total cataract is apparently reached several weeks later than in the experiments using irradiation with 2,000 r.

Comparison of the right and left eyes of the animals treated with cysteine; that is, of the eyes irradiated immediately before or 30 minutes after the introduction of cysteine by

RABBIT NO. 60			101			98			104			117			125		
O.D.	O.S.	T**	O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T
✓	0	1½	✓	✓?	2	✓	✓?	3	✓	✓?	3	✓	✓	3	✓	0	1½
///	0	4	///	✓	2½	///	✓	4	///	✓	7	///	✓	4	///	0	4
///	✓?	6	///	✓	3½	///	✓	8	///	///	9	///	✓?	8			
			///	✓	12												

RABBIT NO. 95			103			107			108			118					
O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T	O.D	O.S.	T	O.D.	O.S.	T			
✓?	0	1	✓	0	6	✓	0	1½	✓	0	1½	///	0	3			
///	0	2	✓	✓?	7	///	✓?	4	///	0	4	///	0	4			
///	✓?	4	✓	0	8	///	0	6									
///	0	8															

* O.D. Irradiated prior to Cysteine injection; O.S. Irradiated 1/2 hour after Cysteine injection.

** T Time after irradiation in weeks.

0 No epilation

✓? Questionable epilation — /// Partial epilation

✓ Slight epilation — /// Complete epilation

Chart 1 (von Sallmann, Dische, Ehrlich, and Munoz). Epilation of lids after one irradiation of 1,500 r given immediately prior to and one-half hour after intravenous injection of two gm. cysteine base.*

became complete within four to eight weeks after irradiation.

In appearance and in time of onset, the signs of radiation damage to the lens were comparable to those described in a previous study in which 2,000 r were used in a single exposure, that is, clinically demonstrable changes began at the equator of the lens, about six to eight weeks after irradiation. Separated from this peripheral ring opacity by a clear interval, clusters of vacuoles then developed which later formed an irregular ring opacity in the posterior cortex.

At the same time subcapsular mosslike opacities became visible in the pupillary area

the intravenous route, revealed marked differences in the degree of epilation of the lids and of cataract formation. The early inflammatory reactions in the anterior segment of the eye, the injurious effect on the corneal epithelium, and the pigment proliferation into the cornea were not altered by pretreatment with cysteine.

The results of this series of experiments in which the rabbits' left eyes were "protected" by intravenous injection of cysteine are illustrated in Figure 7. They were tabulated as far as epilation (chart 1) and radiation damage to the lens (chart 2) were concerned.

Epilation was complete in the right eye of all 11 animals from four to eight weeks after irradiation. Therefore, cysteine injected immediately after the acute exposure to a dose of 1,500 r did not influence the irradiation effects on the lids.

On the other side, none of the eyes which were irradiated 30 minutes after the injection of cysteine showed complete epilation.

RABBIT NO.	60			101			98			104			117		
	O.D.	O.S.	T**	O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T
EQUATORIAL OPACITIES	✓	0	8	✓	0	10	✓	0	8	✓	0	10	✓	0	6
	✓✓	0	10	✓	0	12	✓	0	12				✓	0	8
		✓	21												
OPACITIES IN POST. CORTEX	✓	0	10	✓	0	10	✓	0	14	✓	0	9	✓	0	8
		✓	24	✓✓	0	12				✓	0	10			
SUBCAPSULAR OPACITIES IN ANT. CORTEX	✓✓	0	8	✓	0	10	✓	✓	14	✓	0	10	0	0	8
	✓✓	✓	12	✓	✓	12									
	***	✓	24												

RABBIT NO.	95			103			107			108			125		
	O.D.	O.S.	T	O.D.	O.S.	T	O.D.	O.S.	T.	O.D.	O.S.	T	O.D.	O.S.	T.
EQUATORIAL OPACITIES	✓	0	8	✓	0	8	✓	0	8	✓	0	6	✓	0	5
				✓	0	11				✓	0	8			
OPACITIES IN POST. CORTEX	✓	0	14	✓	0	11	✓	0	10	✓	0	10			
SUBCAPSULAR OPACITIES IN ANT. CORTEX	✓	0	14	✓	0	11	✓	0	10	✓	0	10			

* O.D. Irradiated prior to Cysteine injection; O.S. Irradiated 1/2 hour after Cysteine injection.
** T. Time after irradiation in weeks.
*** Total cataract.
Number of ✓ shows extensity of opacities.

Chart 2 (von Sallman, Dische, Ehrlich, and Munoz). Formation of cataract after one irradiation with 1,500 r given immediately prior to and one-half hour after intravenous injection of two gm. cysteine base.*

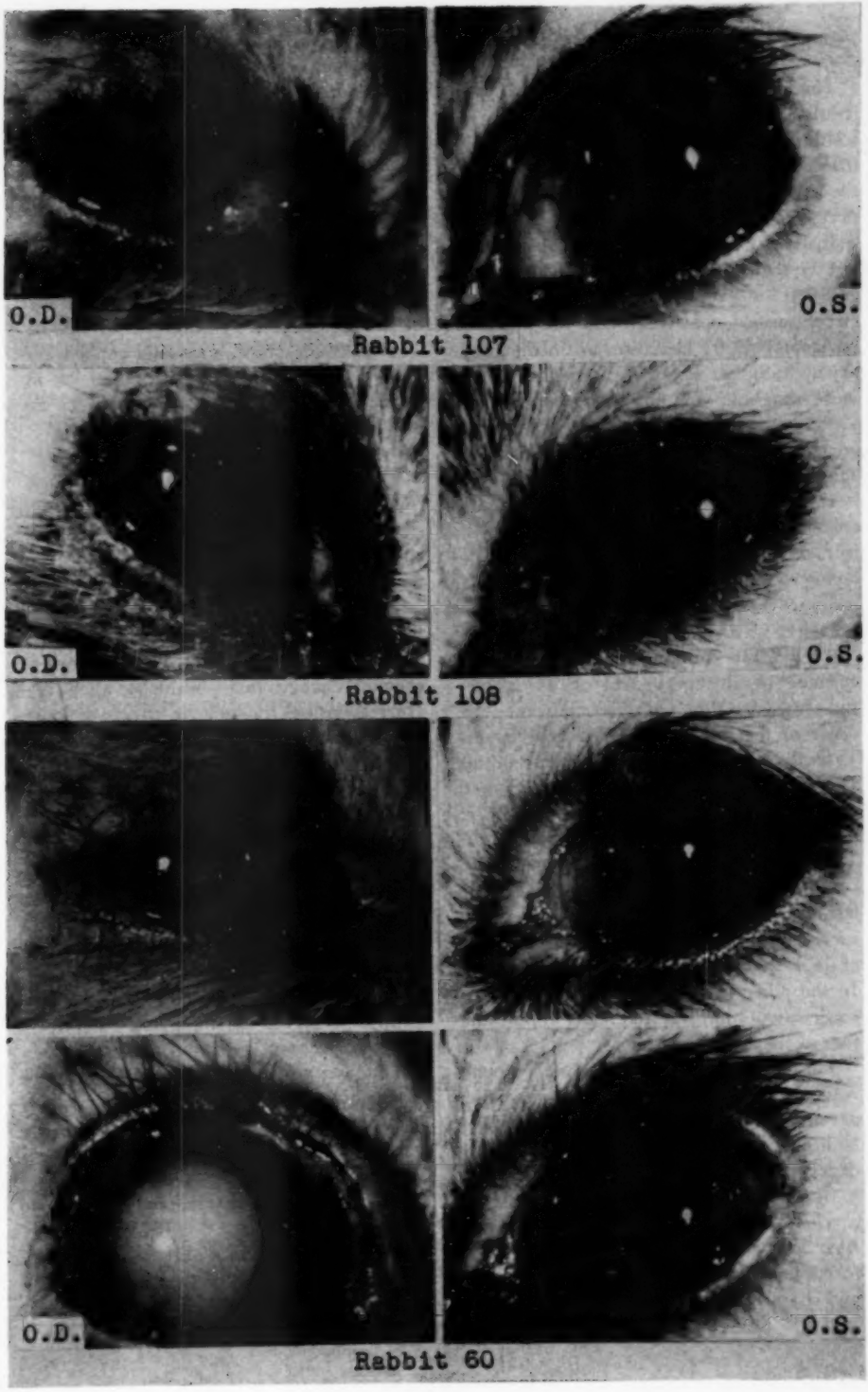
Only once was epilation classified as marked but it was partial. In four instances it was very slight and in three eyes questionable. In the remaining three animals epilation was absent on the left side.

In eyes which had been exposed to 1,500 r prior to the injection of cysteine, cataractous changes developed in the same manner but slightly later than in those observed and described after exposure to 2,000 r. In 10 of the 11 experiments* enough time had elapsed to expect lenticular opacities caused by the X-irradiation. Such opacities were observed in all eyes irradiated before injection of cysteine.

Changes of typical form were either located equatorially or were seen in the anterior or posterior cortex. In one animal the opacity had progressed to a full cataract about five months after irradiation. Obviously the relatively high cysteine level obtained in the aqueous humor, after the dose of 1,500 r was given, did not influence the injurious effect of the X rays on the lens.

* The 11th animal died four weeks after irradiation.

Fig. 7 (von Sallmann, Dische, Ehrlich, and Munoz). Epilation of right and left eyelids irradiated prior to (O.D.) and after (O.S.) intravenous injection of cysteine base. (Rabbit 107) Eight weeks after irradiation. (Rabbit 108) Seven weeks after irradiation. (Rabbit 60) Sixteen weeks and 21 weeks after irradiation.


O.D.
O.S.
Rabbit 107
O.D.
O.S.
Rabbit 108
O.D.
O.S.
Rabbit 60

The left eyes of those animals which were irradiated 30 minutes after intravenous injection of cysteine either presented no ophthalmoscopic signs of radiation damage to the lens or developed a fine opacity at a later period than in the right eyes.

In Rabbit 60 the anterior subcapsular and fine equatorial opacities did not show progression for several months and a transparent circumscribed opacity around the posterior horizontal suture has also remained stationary up to the present. The cataractous lesions were thin and did not interfere with the visibility of the details on the eyeground in contrast to the full cataract of the right eye (fig. 7).

It can be concluded, therefore, that pretreatment of rabbits with cysteine by the intravenous route had at least a marked delaying effect on the development of lenticular opacities produced by irradiation of the eyes with 1,500 r of penetrating X rays.

The results in animals which received cysteine by intraperitoneal or by subconjunctival injection were not tabulated because of the small number of experiments. Typical cataractous changes became noticeable at the same time after irradiation in both eyes of two animals treated with intraperitoneal injection.

In two of the four rabbits treated with a subconjunctival injection of cysteine on the left eye equatorial lens opacities were observed in the control eyes and were lacking at the 15th-week interval in the injected eyes. In the other two animals of this series the observation time was too short for evaluation of the experiment.

The rabbit subjected to cysteine iontophoresis of the left eye prior to irradiation developed radiation damage to the lenses of both eyes at the same time and to the same degree.

In four animals cyanide iontophoresis was carried out on the right eye, 30 minutes before X-ray treatment of both eyes. Equatorial lenticular changes of similar extent and character developed at the same time on the eyes pretreated with cyanide and on the control eyes in two instances.

Longer observation periods are necessary to judge the results in the two other experiments of this short series. It can be concluded from these preliminary experiments that intraperitoneal injection of cysteine and local introduction of cyanide did not seem to exert any protective action against damage of the lens caused by exposure to 1,500 r. The effect of subconjunctivally applied cysteine on retardation or prevention of injury to the lens by X rays cannot be appraised as yet.

Comment

It is not intended in this experimental study to discuss at length the possible mechanisms by which pretreatment with cysteine might have brought about a protective influence against X-ray irradiation damage to the lens.

Since little is known about the nature of chemical changes that—in the last analysis—are responsible for biologic effects of ionizing radiations, a clear understanding of protective influences cannot be expected at the present time.

Chemical changes of a necessarily small percentage producing pronounced biologic effects cannot be considered as an adequate cause of the radiation damage on the basis of the M/N ratio, that is, the relation of the number of ion pairs produced and the number of reacting molecules of a given substance in a biologic system. The possibilities of indirect effects on the solute offer ways of interpretation.

Patt and co-workers concurred with the explanation that activated water reactions lead to inhibition of enzymes. The in vitro observations of G. Barron[7, 8] of inhibition of enzymes requiring –SH groups for activity by ionizing radiations can possibly apply to biologic systems.

On the other hand a shift of the oxydoreductive equilibrium between cysteine and cystine toward cystine in portions of the clear

part of cataractous lenses was shown recently by Dische and Zil. It is possible that an excessive supply of cysteine prior to irradiation may counteract or reduce the disturbance of this equilibrium due to oxidation caused by ionizing radiations.

It might be of significance that, in the experiments reported, radiation effects on two biologic systems were beneficially influenced by the pretreatment with cysteine: the hair in the irradiated area and the crystalline lens. Cystine plays a role in the synthesis of keratin in hair. Furthermore according to the investigations of Dische and Zil one might conclude that balance in the oxydo-reductive –SH systems in the lens are of importance for preserving the integrity of the lens proteins.

Summary

1. Cysteine and cystine penetrate readily from the blood into the aqueous humor to reach equilibrium within a few hours.

2. The highest concentrations of these amino acids in the aqueous humor were obtained with intravenous injection of cysteine after one hour. By this route of administration a ratio of cysteine to cystine greater than one was procured in contrast to the intraperitoneal and peroral use of cysteine. The ratio in aqueous humor was about 1.5 after subconjunctival injection but the absolute value of cysteine was only 10 mg. percent, that is, less than a third of the amount determined after intravenous injection.

3. In in vitro experiments, having the samples stand at room temperature for several hours showed that the oxidation of cysteine to cystine in the aqueous humor progressed at a high rate.

4. Experiments on the protective action of cysteine against X-ray damage to the eye were timed according to the studied appearance curves of cysteine in the aqueous humor. In using a single dose of 1,500 r, epilation of the lids and development of lenticular opacities were influenced beneficially when cysteine was injected intravenously prior to irradiation but they were not changed when the amino acid was administered shortly after the exposure. The epilation effect was strongly reduced and the radiation damage to the lens was at least greatly delayed in the eyes which were "protected" by intravenous cysteine injection.

5. Intraperitoneal injection of cysteine and the iontophoretic introduction of cysteine and of cyanide did not apparently alter the injurious effects of irradiation under the conditions of the experiment.

630 West 168th Street (32).

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STUDIES ON THE OXIDATION OF CYSTEINE TO CYSTINE IN LENS PROTEINS DURING CATARACT FORMATION*

ZACHARIAS DISCHE, M.D., AND HELENA ZIL, B.A.
New York

INTRODUCTION

The most striking chemical change in the lens during the cataractous process is the decrease in sulfhydryl groups; this is evidenced by the decrease and final disappearance of the characteristic nitroprusside reaction[1] when applied to cross sections of the whole lens.

We know that the lens contains two kinds of sulfhydryl groups, those present respectively in the fractions soluble and insoluble in trichloracetic acid, namely in glutathione and in the lens proteins. One of these proteins, the soluble beta crystallin, has been shown to be particularly rich in SH groups.[2]

The decrease of the nitroprusside reaction in cataracts was explained by the gradual disappearance of glutathione and soluble proteins, which occurs during the formation of cataracts. The loss of soluble proteins in the cataractous lens is apparently caused partially by hydrolysis—with subsequent elimination of the breakdown products by diffusion—and partially by precipitation of these proteins.

However, the two extensive changes mentioned above probably represent the last stage of a longer process, initiated by finer changes of certain chemical and physicochemical properties of lens proteins. Opacities of the lens could be the result of these initial, less conspicuous, changes in the chemistry of the lens proteins.

Experience with the behavior of other proteins suggested that, in the initial physicochemical changes and subsequent precipitation of lens proteins during the development of the cataract, an oxidation of SH groups of these proteins may be involved. The activity of many physiologically active proteins depends upon the presence of SH groups; this reactivity is reversibly lost after their oxidation.

Actomyosin,[3] for example, the contractile protein complex of the muscle, contains many SH groups, and loses its ability to contract if these are oxidized. Numerous enzymes reversibly lose their specific enzymatic activities as soon as their SH groups are eliminated by oxidation or combination with certain organic compounds or metals.

The activity of the protein ferritin,[4] a potent vasodepressor, has recently been shown to depend on the presence of SH groups. Their oxidation leads to an inactivation, which can be reversed by certain reducing substances.

On the other hand, it is known that oxidation of SH to –S–S– groups in proteins tends to decrease their solubility by the formation of cross linkages between peptide chains. Conversely keratin,[5] for example, which contains a large amount of cystine but no significant quantity of cysteine, is completely insoluble in this state, but becomes soluble when its –S–S– groups are reduced.

It has been shown by Goldschmidt[6] and by Adams[7] that the sulfhydryl groups of lens proteins can easily be oxidized by oxygen in the presence of glutathione and certain catalysts known to be present in the lens. Since, normally, lens proteins contain a considerable amount of SH groups in spite of the presence of the systems already mentioned, there must be factors in the normal lens which keep at least one part of the SH groups in the reduced state. Under certain pathologic conditions, a shift could occur toward the oxidized side in the equilibrium between the SH and –S–S– groups.

With these ideas in mind, we first de-

* From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University.

termined the content of cysteine and cystine in the soluble proteins of the lens, and also in the insoluble albumoid. The material used consisted of normal lenses of beef, horse, and man and of human cataractous lenses with total and partial cataracts, and also cataractous horse lenses.

We extended our investigations to two species of fish, carp and menhaden, because of two findings: (1) The soluble lens proteins of fish show an immunologic behavior different from those of other vertebrates,[8] (2) they have been reported[9] to contain a much greater amount of sulfur than lenses of other vertebrates.

Since the sulfur content of lens proteins could not be accounted for by the amounts of cysteine and cystine present, we also determined methionine in the soluble and also the insoluble lens proteins.

Preparation of the material

Beef and horse lenses, placed in dry ice shortly after the death of the animal, were obtained in the frozen state from the slaughter house. Fish lenses were obtained in a similar way. The source of normal human lenses was the Eye Bank for Sight Restoration, Inc., where the eyes were stored for several hours in a refrigerator. After extraction, the lenses were preserved in dry ice. The cataractous lenses were obtained from the Institute of Ophthalmology. They were placed in dry ice immediately after extraction.

After 24 hours, the cataractous lenses were thawed out and the stage of the cataract was determined by slitlamp examination. By preliminary experiments, it was demonstrated that this freezing and thawing out of lenses does not cause any opacities. All lenses except those of the horse were stored in the frozen state no longer than three days before analysis. The horse lenses were allowed to remain in the frozen state for several weeks. We found no indication of oxidation of the SH groups.

For the analysis, the lenses were thawed out and homogenized immediately in a Potter Elvehjem glass homogenizer with tenfold amount of either six-percent trichloracetic acid or distilled water, depending on whether total lens protein or certain isolated fractions were to be determined. In the first case the homogenate was centrifuged and the supernatant used for the determination of acid soluble SH and –S–S– groups. The residue from centrifugation was washed twice with large amounts of five-percent trichloracetic acid and then suspended in 6N sulfuric acid, the volume of which was 10 times that of the original lens material. The sulfuric acid suspension was hydrolyzed for 14 hours under reflux.

The distilled water homogenized fraction was centrifuged at high speed at zero degrees. An aliquot of the clear supernatant containing soluble proteins was pipetted off and precipitated with a small amount of concentrated trichloracetic acid. After centrifuging, the trichloracetic-acid soluble extract was used for the determination of acid soluble SH and –S–S– groups, while the residue containing the precipitated soluble proteins was hydrolyzed as above. The insoluble proteins were washed repeatedly using the refrigerated high-speed centrifuge until the supernatant was test free of soluble proteins. The albumoid thus obtained was suspended in tenfold volume of six-percent trichloracetic acid, and the centrifuged residue was hydrolzyed with 6N sulfuric acid.

In some cases the distilled-water lens homogenates were used for the preparation of alpha crystallin, beta crystallin, and albumoid. The isolation of soluble proteins was carried out according to Krause.[11] The proteins were dried by washing repeatedly with alcohol and ether; the latter was driven off in vacuo at 40°C. over phosphorus pentoxide.

Analytical methods

The determination of cysteine, cystine, and methionine in hydrolysates of lens proteins was carried out by a new spectrophoto-

metric micromethod. It is based on a color reaction, previously described,[10] of these substances with glucose and tryptophan in sulfuric acid.

Determination of cysteine

In a test tube (16 by 150 mm.) one cc. of the unknown containing 1 to 10γ of cysteine is added to 0.65 cc. of water. The test tube is put in ice water, and 4.5 cc. of a mixture, previously cooled by standing at room temperature, of six parts of chemically pure, concentrated sulfuric acid (free of arsenic and nitrogen) and one part of a 10 mg. percent glucose solution are added.

Three minutes after the addition of the acid mixture, 0.10 cc. of a 150 mg. percent solution of tryptophan is added, the test tubes are shaken and transferred to a water bath which is at room temperature. After about ten minutes, the tubes are removed from the water bath, wiped off, and allowed to stand at room temperature for four hours.

A standard of cysteine and a blank containing water are prepared in the same way as the sample. After four hours, the density of the unknown solution, as well as that of the standard which has a purple tint, is measured on a Beckmann spectrophotometer at 505mμ, against the yellow-brown blank. This density is proportional to the concentration of cysteine.

Cystine is determined in a similar manner after having previously been reduced to cysteine. This reduction is carried out by mixing the unknown, a cystine standard, a cysteine standard, and a water blank with 20-percent sodium sulfite solution (chemically pure Mallinckrodt) and allowing it to react for 30 minutes at room temperature. The total cysteine now present in the solution is the sum of that present originally and that formed by the reduction of cysteine.

The density of all samples is measured against the blank. The density due to cysteine originally present in the unknown, previously determined, is calculated from the density of the cysteine standard and subtracted from the density of the unknown. The difference, divided by the density of the cystine standard and multiplied by the concentration of the standard, gives the concentration of cystine.

The SH and –S–S– groups in the trichloracetic-acid soluble extracts of lenses were determined in a manner identical with the one already described for cysteine and cystine in protein hydrolysates. On the assumption that cysteine and cystine are represented by the reduced and oxidized glutathione, a glutathione solution was used as standard in these determinations.

Methionine was determined in hydrolysates after oxidation of the cysteine originally present. This was accomplished by allowing the hydrolysate to stand in alkaline sodium carbonate solution for 30 minutes. The unknown contained 10 to 100γ per cc. of methionine. The procedure is the same as for the determination of cysteine, except that the sulfuric acid is mixed with 40 mg. percent glucose instead of 10. After the addition of the sulfuric acid mixture, the test tubes are heated for 10 minutes in a boiling water bath before the addition of tryptophan.

The protein content in hydrolysates was calculated from nitrogen determinations carried out by the semimicro kjeldahl method.

Results

1. Normal lenses

We determined the reduced and oxidized glutathione in the trichloracetic-acid soluble extract, and the cysteine, cystine, and methionine in the total soluble proteins. Similar determinations were also carried out on the isolated alpha and beta crystallin and on the albumoid of normal lenses of beef, horse, carp, menhaden, and man. In addition to the aforementioned color test, methionine was also identified by paper chromatography. The results are listed in Table 1.

A. Glutathione. As can be seen, the trichloracetic-acid soluble of lenses of all four species examined contains no significant amount of oxidized glutathione.

In the lenses of menhaden, the content of glutathione is less than 30 percent of that in the three mammalian lenses.

B. Cysteine and cystine. The content of cysteine in the soluble proteins is several times higher than that of cystine, the ratio varying between 3 and 15. In the reversible oxido-reductive SH system of the soluble proteins, the oxidized components form only 3 to 25 percent of the total. However, this equilibrium is strongly shifted toward cystine in the albumoid. The concentration of cystine here goes up to over 40 percent in the lenses of beef and horse, and to over 65 percent in that of the human.

To exclude the possibility that this shift toward cystine in the albumoid is due to oxidation during the prolonged washing of this insoluble protein, the following experiment was carried out.

TABLE 1

CONCENTRATION OF GLUTATHIONE, CYSTEINE, CYSTINE AND METHIONINE IN NORMAL LENSES OF VARIOUS SPECIES

(The values for glutathione are in mg. percent of total lens while those of the other compounds are in percent protein.)

Species	% Albumoid of Total		Glutathione		Cysteine	Cystine	Sum of Cysteine and Cystine	Ratio of Cysteine / Cystine	Methionine
	Lens	Protein	Reduced	Oxidized					
1. Human (child)	Very small amounts		176.0	0					
Soluble proteins					1.30	0.36	1.66	3.6	
2. Human (child)	Very small amounts		188.4	0					
Soluble proteins							2.26		
3. Human (adult)	10	28	170.0	0					
Soluble proteins					1.81	0.29	2.10	6.02	
Albumoid					0.40	0.73	1.13	0.57	
4. Beef (3–4 yr.)									
Soluble proteins					1.63	0.11	1.74	14.8	3.19
Albumoid					0.64	0.48			
5. Beef (18 mo.)			150.0	0					
Soluble proteins					0.80	0.135	0.94	6.0	
Albumoid					0.34	0.84	1.18	0.40	
6. Horse (old)	10.9		105.0	0					
Soluble proteins					1.44	0.50	1.94	2.9	
Albumoid					0.10	0.81	0.91	0.11	
7. Menhaden			48.5	2.6					
Soluble proteins					2.70	0.73	3.93	3.7	
Albumoid					0.38	2.83	3.31	0.14	
8. Carp									
Soluble proteins							4.17		4.6
Albumoid							2.39		2.68

Eight horse eyes were homogenized and the homogenate was divided into two parts. One part of the homogenate was precipitated immediately with six-percent trichloracetic acid, while in the other, the soluble proteins and the albumoid were separated in the manner described. The cysteine/cystine ratios were determined in the hydrolysates of these two parts. As can be seen from Table 1, the values of the ratio for the total

proteins of the lens lies between those for the two protein fractions. This indicated a higher cysteine/cystine ratio in the albumoid than in the soluble proteins.*

In all species examined, the sum of cysteine and cystine is higher in the soluble proteins than in the albumoid. These greater values in total soluble proteins are exclusively due to the much higher content in cysteine and cystine in the beta crystallin. The SH groups were oxidized during the preparation. Investigations are now under way in order to ascertain the factors responsible for this oxidation of cysteine during the isolation of the crystallins. An attempt is being made to isolate these proteins without oxidation.

In the total soluble proteins of the beef lens, the content in methionine is about 30 percent higher than it is in the albumoid. The

TABLE 2

CONCENTRATION OF CYSTEINE AND CYSTINE IN ALPHA CRYSTALLIN, BETA CRYSTALLIN, AND ALBUMOID OF NORMAL AND CATARACTOUS LENSES OF VARIOUS SPECIES

(The values are reported in percent protein.)

Species	Cysteine	Cystine	Sum of Cysteine and Cystine	Ratio of $\frac{\text{Cysteine}}{\text{Cystine}}$
1. Horse (old normal)				
Alpha crystallin	0.18	0.74	0.92	0.25
Beta crystallin	1.25	0.91	2.16	1.37
Albumoid	0.10	0.80	0.90	0.11
2. Horse (total cataract)				
Alpha crystallin	0.10	0.66	0.76	0.14
Albumoid	0.10	1.40	1.50	0.06
3. Beef (18 mo. normal)				
Alpha crystallin			0.71	
Albumoid			1.18	
4. Menhaden				
Alpha crystallin	0.50	2.00	2.5	0.25
Beta crystallin	0.88	2.60	3.68	0.33
Albumoid	0.38	2.83	3.21	0.13

alpha crystallin of the horse, prepared according to Krause, showed that the sum of cysteine and cystine was practically the same as in the albumoid (table 2).

The alpha crystallin of the beef and menhaden contained even less of these two amino acids than the insoluble proteins. Unfortunately it was not possible to determine the cysteine/cystine ratio in the individual crystallins as they exist before isolation because it was found, as can be seen from Table 2, that in these proteins, which were isolated according to Krause, most of the difference is again due to the much larger amounts of beta crystallin present. If we assume that the soluble proteins of the lens of young adult beef (three to four years old) consists of 60-percent beta crystallin and 40-percent alpha crystallin, then the sulfur content of this protein fraction, calculated from the sulfur values found by Krause[12] in the two pure crystallins, should be 1.03-percent.[11]

As can be seen in Table 1, the value for S calculated from the sum of cysteine, cystine, and methionine in beef lenses is 1.08. This shows that no significant amount of other sulfur-containing components are present in mammalian lenses, and confirms the reliability of our determinations.

* During hydrolysis of the soluble lens proteins with sulfuric acid, no significant oxidation of cysteine takes place. Whether this is also the case with albumoid is now under investigation.

TABLE 3

CONCENTRATION OF REDUCED GLUTATHIONE, TRICHLORACETIC-ACID SOLUBLE -S-S- GROUPS, AND CYSTEINE AND CYSTINE IN NORMAL LENSES AND LENSES WITH TOTAL CATARACTS

(Values for glutathione and soluble -S-S- in mg. percent wet weight of lens; for cysteine and cystine in percent protein.)

Species	% Albumoid of Total		Glutathione	Trichloracetic-acid -S-S- Groups	Cysteine	Cystine	Sum of Cysteine and Cystine	Ratio of Cysteine / Cystine
	Lens	Protein						
1. Human (adult-normal)	10	28	170	0				
Soluble protein					1.81	0.29	2.10	6.20
Albumoid					0.40	0.73	1.13	0.57
2. Human (total cataract)	12.4	54.6	66.5	19				
Soluble proteins					0.24	0.69	0.93	0.36
Albumoid					0.33	1.86	2.19	0.19
3. Human (total cataract)			32.4	15.6				
Soluble proteins					0.21	1.31	1.52	0.16
4. Human (total cataract)	12.3		73.2	38.4				
Albumoid					0.57	2.29	2.86	0.25
5. Human (total cataract)	13.6	60.5	40.2	5.2				
Soluble proteins					0.31	0.72	1.03	0.43
Albumoid					0.53	2.76	3.29	0.19
6. Human (total cataract)			46.3	0				
Soluble proteins					0.22	1.82	2.04	0.13
7. Horse (old normal)	10.9		105	0				
Soluble proteins					1.44	0.50	1.94	2.90
Albumoid					0.10	0.81	0.91	0.11
8. Horse (total cataract)	14.2		8.0	57				
Soluble proteins					0.85	0.66	1.51	0.07

LENSES WITH TOTAL CATARACT

We investigated 10 human lenses with total senile cataracts and two lenses of an old horse with cataract of unidentified origin. The pooled homogenates obtained from two lenses were always used for determinations and, in the case of human lenses, these always came from two different individuals. The results of this series of determinations are listed in Table 3.

A. Glutathione. The reduced glutathione of human cataracts was decreased by 60 to 80 percent while larger amounts of oxidized trichloracetic-acid soluble –S–S– groups were found only in one case. The reduced glutathione disappeared completely in horse cataracts, but a considerable amount of acid-soluble –S–S– groups—corresponding to about 60 percent of the glutathione of normal lenses—was found.

B. Cysteine and cystine. A strong increase in the cystine content of soluble proteins at the expense of cysteine was found in all human lenses. The ratio of cysteine/cystine was between 0.12 to 0.39 in the cataractous lenses while in the normal it lies between 4.0 and 6.0. A similar shift toward cystine was observed in the albumoid, the ratio being 0.19 to 0.24 against 0.51 in the normal lens. The oxidation of cysteine to cystine

was also found in horse lenses, although it was not so pronounced. In the soluble proteins of the cataract, the ratio of cysteine/cystine was 1.3, while that in the normal was 2.9. On the other hand in the albumoid, which in this case was washed with alcohol and ether and dried in vacuo, the cysteine disappeared almost completely.

A more pronounced difference between the albumoid of the normal and cataractous lens appears when the sum of the concentration of cysteine and cystine is considered.

In the normal human lens, this sum was 1.13 percent, in the normal lens of the horse 0.9 percent, and in that of beef it varied between 0.93 and 1.10 percent. In three human total cataracts, the corresponding values varied from 2.2 to 3.3 percent, while in the horse cataracts it was 1.5 percent. In the cataractous horse lenses, the increase in cystine content of the albumoid is more striking when compared with its concentration in alpha and beta crystallin of cataractous and normal lenses.

In the two proteins (table 2) obtained from cataractous eyes, the sum of cysteine and cystine is much lower than in the albumoid; in normal eyes the sum is just as high in the albumoid as in the alpha crystallin but much lower than in beta crystallin.

Partial cataracts

Twelve lenses with nuclear cataracts and eight lenses with cortical cataracts were analyzed. Every lens was divided into an opaque and transparent part. These were analyzed separately and the material obtained from four lenses was pooled for each determination. The results of the analysis are listed in Table 4.

A. Glutathione. The reduced glutathione is decreased in the cataractous portions to about the same degree as in the whole cataractous lens. There is no difference in the level of glutathione in peripheral cataracts between the nucleus and periphery; the same values were also obtained for the nucleus of the nuclear cataracts.

Since the concentration of glutathione is lower in the nucleus of normal lenses than in the cortex, the decrease in the noncataractous nucleus of the peripheral cataract is relatively and absolutely much smaller than in the opaque periphery. In the periphery of the nuclear cataract, the level of reduced glutathione is two to three times higher than in the periphery of the cortical cataract, but it is about 25 to 35 percent lower than in the normal lens.

A significant amount of trichloracetic-acid soluble –S–S– groups was repeatedly ob-

TABLE 4

CONCENTRATION OF REDUCED GLUTATHIONE, TRICHLORACETIC-ACID SOLUBLE -S-S- GROUPS, AND CYSTINE IN TRANSPARENT (A) AND OPAQUE (B) PARTS OF LENSES WITH PARTIAL CATARACTS

(Values for glutathione and soluble -S-S- in mg. percent wet weight of lens; for cysteine and cystine in percent protein.)

Form of Cataract	Glutathione		-S-S-		Cysteine		Cystine		Sum of Cysteine and Cystine		Ratio of Cysteine / Cystine		% Albumoid in Total Lens	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
1. Nuclear	196	72	1.5	104										
Soluble protein					0.40	0.17	0.81	1.30	1.21	1.47	0.33	0.13	6.59	21.4
Albumoid					0.23	0.26	1.15	2.05	1.38	2.31	0.19	0.13		
2. Nuclear	128	36.4	19.8	51.2										
Soluble protein					0.35	0.18	1.17	1.80	1.52	1.98	0.30	0.10	4.8	15.8
Albumoid					0.36	0.13	0.72	2.06	1.08	2.19	0.33	0.06		
3. Peripheral	60.0	80.5	3.0	18.0										
Soluble proteins					0.27	0.22	1.25	1.05	1.52	1.27	0.20	0.18	10.5	13.2
Albumoid					0.39	0.40	0.89	1.10	1.28	1.50	0.44	0.36		
4. Nuclear	148.2	23.2	0	36.2										
Soluble proteins					0.4	0.84	0.92	2.16	1.32	3.00	0.43	0.40		
5. Peripheral	35.6	76.5	14.9	3.0										

served in the nucleus of the nuclear cataracts. It has not been possible, as yet, to decide whether these –S–S– groups are oxidized glutathione or cystine from hydrolyzed proteins.

B. Cysteine and cystine. In lenses with partial cataract the shift from cysteine to cystine in the soluble proteins is very marked, both in the cataractous and noncataractous parts. The ratio of cysteine/cystine is considerably less than one and, in the cataractous parts, it is as low as in the total cataract. In the noncataractous periphery, however, this ratio is on the average slightly higher than in the cataractous parts. As far as the change in the state of oxidation of the oxido-reductive SH system of the proteins is concerned, the noncataractous parts of lenses with partial cataracts do not differ significantly from the total cataracts.

The second characteristic change observed in lenses with total cataract—namely, the increase in the sum of cysteine and cystine in the albumoid—was not found in the noncataractous parts. This increase is very pronounced in the cataractous nucleus and less marked but present in the cataractous periphery.

Discussion

Our investigations have revealed three changes in the composition of lens proteins during the development of senile cataracts. These changes seem to be related to each other and to the pathogenesis of the disease.

1. We found that the equilibrium between sulfhydryl and disulfide groups in the soluble protein of normal lenses lies toward the reduced compound, four to six times as much cysteine as cystine being found in these proteins. During the cataractous process the amount of cystine increases at the expense of cysteine, so that the ratio of cysteine to cystine is reversed. At the same time, the sum of cysteine and cystine either remains unchanged or decreases. Therefore, the shift from cysteine to cystine must be due to the oxidation of SH groups of soluble proteins.

2. The ratio of cysteine/cystine in the insoluble proteins of the normal lens is much smaller than that in the soluble proteins and declines in the cataract. The sum of cysteine and cystine increases in the cataractous albumoid and, in the advanced stage of the disease, reaches values more than three times as high as in the normal.

3. This increase in the sum of the two amino acids is accompanied by an absolute increase in the concentration of albumoid in the cataractous lens (table 3). This seems also to be demonstrated by the fact that (table 4) in nuclear cataracts the concentration of albumoid is higher in the nucleus than in the periphery, while the opposite is the case in peripheral cataracts.

Furthermore, our data indicates that the oxidation of SH groups of soluble proteins and the change in the concentration and composition of the albumoid do not take place simultaneously but that the oxidation precedes the change. This is illustrated by the fact that, in the transparent part of the nuclear cataract, we find the soluble proteins to be largely in the oxidized state, without any pronounced change in the composition of the albumoid.

To evaluate the possible significance of these findings for the pathogenesis of cataract, we have to recall two other facts which have been established previously and appear confirmed by our own determinations:

1. Beta crystallin contains considerably more cysteine and cystine than either the albumoid and alpha crystallin, which do not differ in their content of the two amino acids.

2. The cataractous process is accompanied by a considerable decrease in the amount of soluble proteins in the lens, which may be partly due to hydrolysis and partly to precipitation of these proteins.

In the light of these two facts, the considerable increase in the sum of cysteine and cystine in the albumoid of total cataract strongly suggests that either beta crystallin or a sulfur-rich product of its hydrolysis is precipitated during the formation of the

cataract. This deposition of an nonphysiologic insoluble protein in the lens fiber may lead to loss of transparency.

The fact that the oxidation of soluble proteins preceded the increase of cystine in the albumoid suggests the possibility that this oxidation is one of the factors which cause the precipitation of the soluble proteins. The oxidation of SH groups of proteins could cause their precipitation with loss of transparency, either directly by decreasing the stability of proteins in solution or indirectly by sensitizing the proteins against precipitating agents (or possibly to proteolysis yielding insoluble sulfur-rich breakdown products).

Further investigations are necessary to decide this question. It is clear, however, even now, that the oxidation of soluble proteins cannot cause opacities by itself, because the process of oxidation is far advanced in the transparent periphery of nuclear cataracts. An additional factor must enter into play to produce the opacities.

This could be the decrease in the amount of reduced glutathione. The reduced glutathione concentration is much lower in total cataracts and in the opaque parts of cortical cataracts than in the periphery of nuclear cataracts. The occurrence of opacities in the lens would therefore require the concurrence of the oxidation of soluble proteins and the elimination of the glutathione below a certain minimum value.

Whatever may be the significance of the oxidation of SH groups or soluble proteins for the cataractous process, we have to assume that, in the normal lens, one or more factors are present which prevent this oxidation. This conclusion appears unavoidable in view of the fact that the normal lens contains a system which can promote the oxidation of SH groups in proteins by oxygen. This system consists of ascorbic acid, glutathione, and certain catalysts.

The permanent oxidation of cysteine of soluble proteins—as it appears in the cataract—could be prevented in normal lens: (1) Either by some structural factors barring the oxidizing systems from its substrate, (2) by certain inhibitors, (3) or by reducing substances, produced in the lenticular metabolism, which are able to convert –S–S– groups of proteins to SH groups. The breakdown of this protective agent or these structural conditions would then release the cataractous process.

Our concept of the origin of cataract disagrees in some respects with that put forth by Krause. He assumes that shifts in the pH of the lens initiate the cataractous process by releasing activity of the lens proteinases. This would lead to hydrolysis of beta crystallin, while alpha crystallin is precipitated and thus increases the amount of albumoid. This hypothesis is based on the fact that the pH of the lens shifts in cataracts toward the acid side.

During prolonged autolysis of normal lens tissues at pH 6 to 7, the albumoid increases by about the same amount as alpha crystallin decreases. It is possible that the decrease of the pH in cataracts could be the result of protein hydrolysis, and it would therefore be necessary to prove that shifts in pH precede the onset of the cataractous process.

On the other hand changes in the pH could lead to a shift of the oxido-reduction potential of the lens resulting in the oxidation of cysteine. The parallelism between the increase in albumoid and decrease of alpha crystallin during lenticular autolysis might only be an apparent one. The increase due to beta crystallin could be masked by a simultaneous hydrolysis of albumoid; otherwise, it would be difficult to understand the increase in cysteine and cystine in the albumoid of cataractous lenses.

Our observations were restricted to human senile cataracts and probably senile cataracts in the horse. It remains to be established whether the same conditions prevail in other forms of cataracts, especially the experimental ones—for example, of toxic origin

and galactose cataract. Investigations to test the validity of our hypothesis are being continued.

Summary

1. Soluble proteins of normal lenses contain much more cysteine than cystine.

2. The oxido-reductive equilibrium between the two amino acids is shifted toward cystine in lenses with senile cataract.

3. This shift already appears in the non-opaque portions of partial cataracts.

4. The sum of cysteine and cystine in the albumoid is considerably increased in total cataracts.

5. The possible significance of these changes for the pathogenesis of cataract is discussed.

630 West 168th Street (32).

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THE AQUEOUS: PLASMA STEADY-STATE RATIOS*

Their variations and significance

John E. Harris, M.D., and Leta B. Gehrsitz, M.S.
Portland, Oregon

An intriguing problem of ocular physiology is to explain the observation that many substances are present in lower concentration in aqueous than in plasma water; that is, their aqueous:plasma steady-state† ratios are less than 1.0.

Among the compounds which show this aqueous deficit are the normally present glucose and urea,[1] and such injected substances as galactose and the pentoses, xylose and arabinose,[2] fructose,[3] and para-amino hippuric acid, Rayopake, and Diodrast.[4]

Since most of these compounds have no metabolic function in the species studied, their deficit is not due to intraocular utilization. Moreover, we have presented evidence which indicates that the monosaccharides, at least, are not actively transferred across the blood-aqueous barriers, nor is there evidence of an active transfer of the other compounds listed.

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† The steady-state ratio is the ratio of the aqueous to the plasma concentration when these concentrations show no demonstrable change with time. If at a true equilibrium, the ratio would be 1.0. von Bertalanffy[5] speaks of a steady-state as the property of an open system to which materials must be continually added. This aptly describes the aqueous.

The feature common to the creation of the deficit appears to be a partial "filtering out" of these substances from the plasma when the aqueous is formed. This requires work which may be either hydrostatic—that is, capillary pressure—or osmotic.

Hydrostatic work is not sufficient to supply the total energy needed. Therefore, the maintenance of a steady-state ratio below 1.0 is tentatively considered to result from the osmotic work done by a substance which is present in the aqueous in higher concentration than would be predicted from a true equilibrium, assuming the activity coefficients to be equal in aqueous and plasma. This higher concentration may result either from the active transfer[‡] of any substance, or from the increase in osmotic activity which accompanies the metabolism of intraocular structures, particularly the production of lactic acid from glucose.

Discounting hyaluronic acid, available analyses of rabbit aqueous indicate that only ascorbic acid and lactic acid are present in higher than predicted concentrations. Therefore, the active transfer of the former and the metabolic production of the latter are the most likely sources of energy for the accomplishment of osmotic work.

We have shown[2] that the active transfer of ascorbic acid alone can account for the steady-state ratios of glucose and urea observed at physiologic concentrations. However, if the plasma level of one of these "filtered out" substances is raised, the amount of work required will be greater if the low steady-state ratios are to be maintained.

It was the purpose of the investigations reported in this paper to determine whether the active transfer of ascorbic acid and production of lactic acid can supply the required energy when the plasma concentrations of these nonelectrolytes is raised.

Accordingly, we have studied, in the rabbit: (1) The relationship of the steady-state ratios of monosaccharides to the plasma concentration, (2) the response of the ascorbic-acid active transfer mechanism when an osmotic load is put on the system, and (3) the rate of uptake of ascorbic acid when the plasma level is raised. Since the aqueous ascorbic-acid concentration of the cat is low and since there is evidence that sodium chloride is secreted in this animal,[7] we have also studied the variation of the steady-state ratios with the plasma concentration in the cat, to provide a comparison with the rabbit.

Methods

The coefficients of transfer from plasma to aqueous were determined in the manner previously described.[2]

Xylose and arabinose were chosen as the test substances for the steady-state ratios to obviate any question of intraocular utilization. Using a constant injection machine, the sugars were injected intravenously in varying concentrations and at varying rates. The variations in rate necessary to produce the individual plasma levels desired were determined empirically.

It was found that a sufficiently constant plasma level could be maintained for slightly over four hours. Beyond that time the level was quite unpredictable and thus unreliable. Consequently, all aqueous samples were taken at about four hours. Calculations indicate that this time is sufficient to achieve about 99 percent of the true steady-state ratios at low plasma concentrations, while

‡ When referring to a single substance, the term "active transfer" is preferred to "secretion," since the latter term is used frequently to define the elaboration of bulk fluid. The concept of active transfer requires that the substance be present in higher activity in the formed than in the parent fluid. Active transfer of an ion represents an increase in electrochemical potential.[6] Formulation of this concept includes an additional factor—that is, the difference in electrical potential between the two sides of the membrane. The distinction is useful when one is endeavoring to determine whether one or both ions of a salt are actively transferred and in computing the total energy expenditure required. The potential difference, as a factor, will cancel when both ions of a salt are considered. We have restricted our usage to one of an actual increase in chemical potential or activity, since this is essential for the formation of a fluid dilute in various solutes.

in high concentrations only about 90 percent of the ultimate ratio may be reached.

Sugars were determined by the method of Somogyi[8] on filtrates from which glucose had been removed by fermentation with yeast.

Ascorbic acid was determined by titration with 2,6 dichlorophenolindophenol. The filtrates of blood and aqueous were so prepared as to bring the metaphosphoric acid concentration to 2.5 percent.

Rate of transfer of xylose and arabinose into aqueous

As a preliminary to determining the steady-state ratios, a knowledge of the rate of transfer from plasma to aqueous is needed so that the extent of the approach to a true steady-state can be calculated. The data are given in Table 1.

The values* for the rabbit were taken from a previous publication.[2] They show that arabinose entered at a somewhat slower rate than xylose in the rabbit and somewhat more rapid rate in the cat. The difference was not great as permeability figures go but was statistically significant. The reason for the difference is not known. The blood-aqueous barriers appear to have a selective permeability and the rate of entrance of various compounds does not follow their molecular size.[9]

A true comparison of the rates of transfer of these compounds between the rabbit and cat is not possible unless one knows the surface area across which the diffusion takes place and the volume of the aqueous. The difference between species does not appear to be great, however.

Steady-state ratios of xylose and arabinose

The aqueous:plasma steady-state ratios of xylose and arabinose in the rabbit showed a marked variation with plasma concentration (figs. 1 and 2). As the plasma concentration of these pentoses was raised above five mM. per liter, a gradual increase in the steady-state ratio was noted. Below that level, the ratio dropped markedly. The curve is not that which would be expected if the total work done remained constant, although there is some similarity.

In contrast to the rabbit, the steady-state ratio remained virtually constant as the plasma level of these sugars was raised in the cat (figs. 3 and 4). It is, of course, possible that the steady-state ratios might have fallen if the plasma levels were lowered sufficiently. However, we tested considerably lower concentrations in the cat than in the rabbit and reached the lower limits of accuracy of available analytical techniques. It

TABLE 1

Coefficient of transfer (k_1) from plasma to aqueous

	d-Xylose	l-Arabinose	Difference between means*
Cat	Mean $=0.78\times10^{-2}$ (5 animals) S.D. $=\pm0.16\times10^{-2}$	Mean $=1.08\times10^{-2}$ (6 animals) S.D. $=\pm0.19\times10^{-2}$	Significant
Rabbit	Mean $=2.84\times10^{-2}$ (5 animals) S.D. $=\pm0.35\times10^{-2}$	Mean $=2.04\times10^{-2}$ (9 animals) S.D. $=\pm0.49\times10^{-2}$	Significant

* Calculations were made using Student's t test with $P=0.05$.

* In the paper quoted[2] we noted that the calculated value, k_1, varied somewhat with the time of drawing of the first aqueous. This we attributed to the fact that the sugar did not distribute itself equally throughout the large volume of aqueous. The values here presented were calculated from data taken over the same time period. The difference is not great and does not alter our previous conclusions.

can be seen that the steady-state ratio for arabinose is slightly lower than that for xylose in both the cat and rabbit. While the steady-state ratios may depend to a certain extent on the permeability of the barriers, this is certainly not the entire factor.

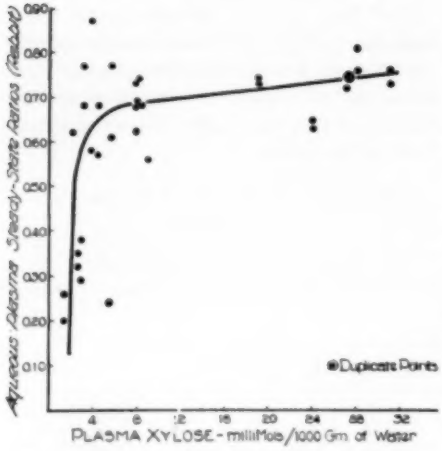

Fig. 1 (Harris and Gehrsitz). Variation of the aqueous:plasma steady-state ratio with the xylose plasma concentration in the rabbit. Each point represents the value of one eye. A concentration of 32 mm./L. is the osmotic equivalent of 575 mg.-percent glucose.

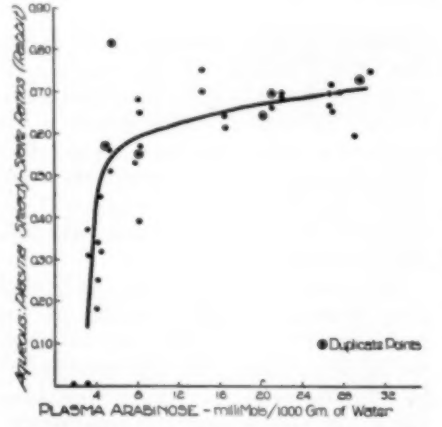

Fig. 2 (Harris and Gehrsitz). Variation of the aqueous:plasma steady-state ratio with the arabinose plasma concentration in the rabbit. Each point represents the value for one eye.

Effect of osmotic load on ascorbic acid of aqueous

Since the injection of these compounds puts an increased work load on the aqueous forming system, it seemed advisable to investigate the response of the ascorbic-acid active transfer mechanism to this increased load.

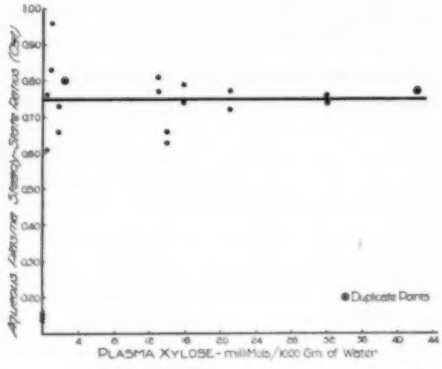

Fig. 3 (Harris and Gehrsitz). Variation of the aqueous:plasma steady-state ratio with the xylose plasma concentration in the cat. Each point represents the value of one eye.

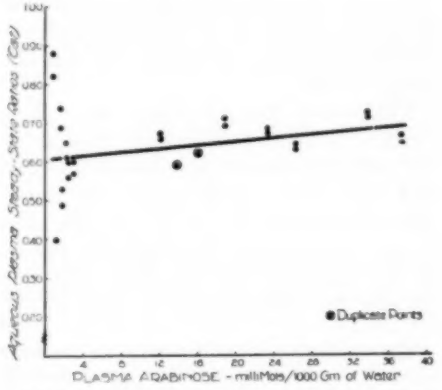

Fig. 4 (Harris and Gehrsitz). Variation of the aqueous:plasma steady-state ratio with the arabinose plasma concentration in the cat. Each point represents the value for one eye.

Accordingly, we have measured the effect of the intravenous injection of xylose and arabinose on the ascorbic-acid concentration of the aqueous. The procedure was similar to that described for the determination of the steady-state ratios. An initial aqueous sample was taken. Then, after a four-hour period of injection of xylose or arabinose, the second aqueous sample was taken from the other eye. This period of injection is needed to achieve a relative osmotic balance. The results are given in Table 2.

The injection of the sugar invariably caused a rise in the ascorbic acid content of the aqueous. In a few instances we also followed the level of the plasma ascorbic acid and noted an increase in this value on injection of the sugars. (These sugars do not interfere with the ascorbic-acid determination.)

Kinsey[10] has shown that, as the plasma ascorbic-acid level is raised, the aqueous level likewise rises so that a constant ratio of aqueous to plasma is maintained up to a certain point. Thus, the rise in ascorbic acid we noted is attributable to the increase in plasma ascorbic acid, rather than to any inherent response of the aqueous-forming system. Nevertheless, additional work per liter of aqueous formed is thereby made available.

Rate of uptake of ascorbic acid by aqueous

The work done in the active transfer of a substance can be computed in terms of the number of calories required per liter of fluid formed or the number of calories required per unit time. Having determined

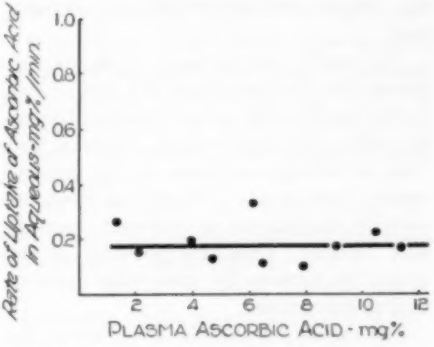

Fig. 5 (Harris and Gehrsitz). Variation of the rate of uptake of ascorbic acid from plasma to aqueous with variation of plasma concentration (rabbit).

TABLE 2

Effect of constant injection of various sugars for four hours on aqueous ascorbic acid concentration

Aqueous Ascorbic Acid			Plasma Ascorbic Acid	
Preinjection (mg. %)	Postinjection (mg. %)	Percent Increase	Preinjection (mg. %)	Postinjection (mg. %)
19.1	24.3	27		
17.6	23.9	36		
18.5	21.1	14		
15.2	17.4	14		
23.1	26.0	13		
15.8	21.4	35		
13.0	19.7	52		
27.0	37.4	39		
17.8	21.6	21	0.54	0.32
18.5	25.1	36	0.32	0.56
11.6	17.8	53		
24.6	35.0	42	0.53	0.70
20.4	22.8	12	0.29	0.40
24.6	35.5	44	0.66	0.98
22.6	30.7	36	0.67	1.06
Avg. 19.3	25.3	31	0.50	0.67

that the work expended per liter of formed aqueous in the active transfer of ascorbic acid increased only moderately when an osmotic load was imposed, we became interested in determining whether the work done per unit time can be greatly altered.

Ascorbic acid was injected in graded doses intraperitoneally and intravenously and its rate of uptake in the aqueous measured, generally, between 20 and 40 minutes after the injection. Figure 5 shows that the rate of uptake of ascorbic acid in the aqueous was independent of its plasma concentration.

The results are consistent with the conclusion that the work done per unit of time by the system in the active transfer of ascorbic acid is relatively constant. Together with those of Kinsey and those of the previous section, these results indicate that the active transfer mechanism is normally working near capacity. Thus, the potential of this system to increase the intraocular pressure is definitely limited.

The results corroborate the concept that ascorbic acid is actively transported into the aqueous. Active transfer of ascorbic acid into the aqueous appears to be like some other metabolic processes. The rate of uptake or utilization is quite independent of the concentration within the limits studied.

Discussion

The work balance for the rabbit can be calculated in the manner previously described.[2] Using the data from Table 2, the work performed in the transfer of ascorbic acid is determined to be 2.5 calories per liter of aqueous. Under an osmotic load this is increased by 31 percent to 3.3 calories per liter. Assuming a plasma lactic acid of 10 mg. percent and an aqueous :plasma ratio of 2:1, an additional 0.8 calories are provided.

Both of these acids have low pK values, 4.20 for ascorbic acid[11] and 3.6 for lactic acid.[12] (The second pK of ascorbic acid is so high that it need not be evaluated.) Thus, at physiologic pH, both acids can be considered to be present as the monovalent salt.

Assuming this to be the sodium salt, an additional 1.2 calories are required. Thus the total energy available for osmotic work is approximately 5.2 calories per liter of aqueous.

From the data given in Figures 1 and 2 for the rabbit, the maximum osmotic work required for the maintenance of the steady-state ratios is at the highest plasma concentrations and can be calculated to be 4.1 calories per liter of aqueous for xylose and 4.4 calories per liter for arabinose. Both of these values represent conservative maxima, because the true steady-state value is not reached at four hours. If the measured steady-state ratio were only 90 percent of the true value, the work done in the dilution of arabinose would be 3.7 calories. Thus, the maximum work required for the arabinose dilution lies somewhere between 3.7 and 4.4 calories.

One can conclude, therefore, that in the rabbit the active transfer of ascorbic acid and the metabolic production of lactic acid can account for the lowered steady-state ratios observed. No further source of work need be sought.

By contrast, the work done in the dilution of the pentoses in the cat is not provided by the active transfer or production of these acids. Some other source of energy must be provided. The active transfer of sodium chloride is the most likely.

An active transfer mechanism of sodium chloride should have a much greater work potential than that of ascorbic acid. This greater work capacity may account for the constant steady-state ratios observed when the plasma level of the pentoses is raised in the cat.

While the active transfer of ascorbic acid and the production of lactic acid may account for the low steady-state ratios observed, these substances are not present in sufficient quantities to exert the excess osmotic pressure of aqueous over plasma that has been reported.[13,14] This excess osmotic pressure of

the aqueous is equivalent to 3 to 5 milliequivalents of sodium chloride per liter, sufficient to exert a hydrostatic pressure of up to 150 mm. Hg.

The reason why this osmotic pressure difference is not manifest as an intraocular pressure of that magnitude is not answered by any known data. A drainage off at a level of 20 mm. Hg would not account for the discrepancy since the barriers are freely permeable to water and the osmotic concentration should then be the equivalent of 20 mm. Hg.

However, a substance can, feasibly, be actively transferred into the aqueous in sufficient concentration to create a higher osmotic pressure as measured in vitro than is manifest in vivo, if the rate of turnover of the substance is so rapid relative to water that osmotic equilibrium is never achieved. This possibility should be evaluated for sodium chloride in the cat and dog. Also it is possible that osmotic pressure measurements, in vitro, do not precisely reflect the pressures exerted in vivo.

Other than the fact that the work requirements must be met, the mechanisms by which any steady-state ratio is achieved are not known. Kinsey and his collaborators,[15] working with the rabbit, have postulated that a particular steady-state is determined by the balance between a coefficient of flow and a coefficient of transfer or diffusion of the substance from plasma to aqueous. Their formulation specifies that the steady-state ratios remain constant as the plasma level is varied unless an alteration of the coefficients is postulated.

By definition, the coefficient of diffusion must remain constant. From their formulas, it can be calculated that a decrease in the steady-state ratio from 0.70 to 0.25, such as we noted, would require a seventy-fold increase in a coefficient of flow. A constant that could undergo such variations has no meaning. Thus their mathematical treatment and their conclusions drawn therefrom do not appear to be valid.

Summary

1. In the rabbit, the steady-state ratios of xylose and arabinose were found to increase as the plasma concentration was raised. In the cat, however, the steady-state ratios remained constant over a wide range of plasma concentrations.

2. Both the plasma and aqueous ascorbic-acid levels were found to rise when the sugars were injected into the rabbit.

3. The rate of uptake of ascorbic acid is independent of the plasma level of this substance.

4. In the rabbit, the active transfer of ascorbic acid and the production of lactic acid supply sufficient osmotic activity to account for the steady-state ratios of xylose and arabinose within the range studied. In the cat, some other source of energy is required.

5. The active transfer of ascorbic acid into the aqueous of the rabbit is normally functioning near capacity.

3181 S.W. Marquam Hill Road (1).

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FURTHER STUDIES ON CHOLINESTERASE ACTIVITY IN OCULAR TISSUES*

ANDREW DE ROETTH, JR., M.D.
New York

In a previous communication[1] cholinesterase activity was demonstrated in ocular tissues and fluids of normal experimental animals. The purpose of the present investigation is to illustrate the physiologic importance of this enzyme in the eye.

PART I

ANTICHOLINESTERASE AGENTS

INTRODUCTION

A great variety of substances have known anticholinesterase properties, and of these enzyme inhibitors the so-called reversible inhibitors, eserine and prostigmine, have been used for many years. Lately attention has been centered on the irreversible inhibitors, mainly di-isopropyl fluorophosphate (DFP) and tetraethyl pyrophosphate (TEPP). Nachmansohn[2, 3] and Rothenberg, Koelle and Gilman,[5, 6] and others[7] have reviewed the action of DFP on cholinesterase and the chief characteristics of this reaction may be outlined:

1. By definition DFP is an irreversible inhibitor, but this inactivation process depends on several factors such as time, temperature, inhibitor concentration, circulation, permeability of the different cell membranes, rates of penetration and diffusion, and others.

2. The inhibition of the enzyme by DFP takes place on a mole to mole basis.

3. DFP penetrates very poorly in the living cell, and only a fraction of the outside concentration of this inhibitor finds its way into the cell; this intracellular part has been estimated as 0.5 percent of the outside concentration.

The actions of DFP on the eye have been investigated extensively from the ophthalmic point of view by Leopold and Comroe,[8] Scholz and others,[9, 10] and von Sallmann,[11] and it is not the purpose of this study to review their findings or to duplicate their laboratory results.

DFP, however, besides being an effective therapeutic agent in certain ocular diseases, also lends itself to the study of the physiologic function of cholinesterase in the eye.

* From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital. Supported by the Knapp Memorial Foundation.

There are only a few sites in the body where one can conduct in vivo experiments to correlate cholinesterase activity with normal function of the organ, and, since the eye happens to be such a site, the following experiment was carried out.

Technique

One drop of 0.2-percent DFP in peanut oil was instilled in 65 normal rabbit eyes, which was the same dosage as used previously by von Sallmann and Dillon,[11] and also approximately the same amount as administered clinically in the treatment of certain types of glaucoma; 35 eyes served as normal controls.

One drop of 0.2-percent DFP contains approximately 140 μg. of DFP, but because of too many variables and unknowns it would be impossible to estimate the amount of DFP that actually penetrates to the iris sphincter.

At stated intervals the animals were killed, the eyes enucleated, dissected, and the tissues weighed.

The iris and ciliary body, removed in one piece, was washed for two hours in normal saline solution to remove the excess DFP that accumulates on the outside of the cells. If this step had been omitted, in the homogenization which followed the enzyme would have come in contact with the excess extracellular DFP and thus been destroyed, presenting a false picture of the state of enzyme inhibition. As previously mentioned, only a fraction of the extracellular DFP penetrates into the cell, and the greater part which remains outside can be washed away.

Then the cholinesterase activity of the washed tissues was determined in the manner described in a previous communication.[1] Size and reaction of the pupil of six of these DFP-treated eyes was measured cinematographically according to the method of Lowenstein.[12] Cholinesterase content of the normal iris and ciliary body was expressed as 100 and the enzyme activity of the DFP-treated tissues was calculated as percentages of the normal control.

Results

Figure 1, representing 100 eyes, of which 35 were normal controls, indicates that, within the first half hour following DFP instillation, the cholinesterase content of the iris and ciliary body drops to slightly less than 15

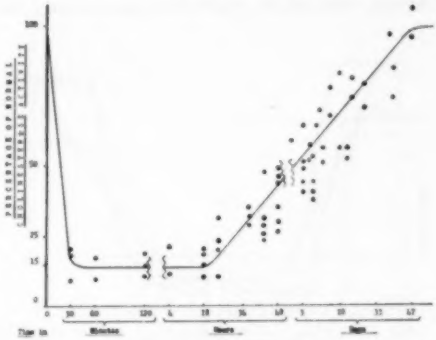

Fig. 1 (de Roetth). DFP experiment. The solid line represents the average cholinesterase activity (expressed in percentage of normal) of the irises and ciliary bodies of 65 rabbit eyes following instillation of one drop of 0.2-percent DFP.

percent of normal and remains at this low level for 18 hours, after which it starts to increase again.

This rate of recovery is parabolic; 50 percent of activity returns within the first week, but full recovery takes seven to eight weeks. Since DFP is an irreversible enzyme inhibitor, it may be assumed that the rate of recovery, as shown in Figure 1, represents the rate of resynthesis of cholinesterase in the iris and cillary body of the rabbit.

Figure 2, representing the pupillograms of six rabbits, shows that maximal miosis occurred within the first 15 minutes, the pupillary diameter constricting on the average from a normal 6.5 mm. down to 2.0 mm. This maximal miosis was maintained for 18 hours, at which time the pupils rapidly increased in size returning to normal in 48 hours.

The pupillary light reflex showed similar changes; all six rabbits manifested a normal light reaction before treatment but, following

instillation of DFP, the light reflex disappeared within 15 minutes and was absent for 18 hours; it then started to recover and became normal again in 48 hours.

In Figure 3, the averaged pupillograms, drawn as one curve, are superimposed on the chemical data as shown in Figure 1. This shows that when cholinesterase activity in

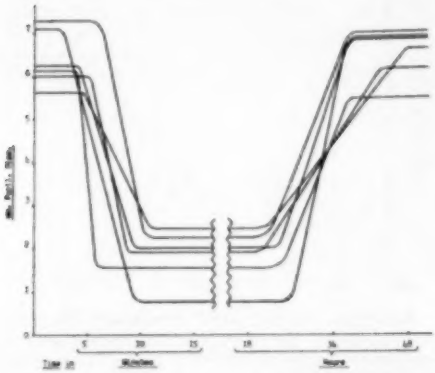

Fig. 2 (de Roetth). DFP pupillograms. Pupillary diameters of six rabbit eyes following installation of one drop of 0.2-percent DFP.

the iris and ciliary body of the rabbit drops below 15 percent of normal—as was the case for the first 18 hours following DFP instillation—the pupil ceases to function; however, as soon as enzyme activity goes above 15 percent, normal pupillary function rapidly returns.

Discussion

It is a general rule in enzyme chemistry that most enzymes exist in excess throughout the body. The present in vivo experiment, while bearing out this general rule in the case of the iris and ciliary body of the rabbit, demonstrates, however, that a certain minimum amount of this enzyme, about 15 percent is nevertheless essential for normal pupillary function.

This observation is of general physiologic interest, because it is difficult to test concurrently for normal physiologic function and for cholinesterase activity in other parts of the body.

Nachmansohn[13] noted similar results using frog's sciatic nerve and the abdominal chain of nerves of the lobster. After incubating these nerve preparations with DFP for varying lengths of time, he measured the action potential with the cathode-ray ossilloscope and demonstrated that the reversibility of the action potential is parallel to the amount of cholinesterase which reappears in these nerve preparations.

Summary

1. Cholinesterase occurs in excess in the iris and ciliary body of the rabbit; but 15 percent of the total amount is necessary for normal pupillary function.

2. The rate of recovery of cholinesterase activity after inhibition by DFP probably represents the rate of resynthesis of this important enzyme in the iris and ciliary body.

3. The physiologic significance of the enzyme was demonstrated by paralleling the cholinesterase activity of the iris and ciliary body with the functional state of the pupil.

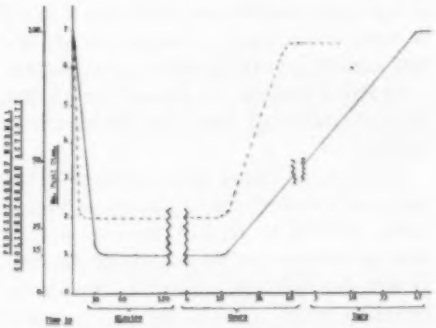

Fig. 3 (de Roetth). The solid line represents the average cholinesterase activity (expressed in percentage of normal) of the irises and ciliary bodies of 65 rabbit eyes following instillation of one drop of 0.2-percent DFP. The broken line represents the average pupillary diameter of the six DFP-treated rabbit eyes.

Part II

Retrobular alcohol injection

Introduction

While the clinical use of retrobular alcohol injections for painful blind eyes is a well known and widely employed therapeutic procedure, very little work has been done on experimental retrobulbar alcohol injections. In a recent publication Kornblueth[14] reported extensive clinical, histologic, and chemical studies on rabbit eyes following retrobulbar alcohol injections. Since I believed that retrobulbar alcohol injection could be used to study the functional significance of cholinesterase in the rabbit iris and ciliary body, the following experiment was carried out.

Technique

The technique was similar to that described by Kornblueth;[14] under intravenous nembutal anesthesia 0.3 ml. of 95-percent alcohol was injected into the left orbits of 20 normal adult rabbits, the right side serving as normal control. Kornblueth injected 0.25 ml. of 95-percent alcohol; however in the present study the higher dosage was used purposely because preliminary experiments showed that with the lesser amount the results were somewhat inconsistent; on the other hand, more than 0.3 ml. usually caused excessive irritation, as well as a purulent conjunctival discharge.

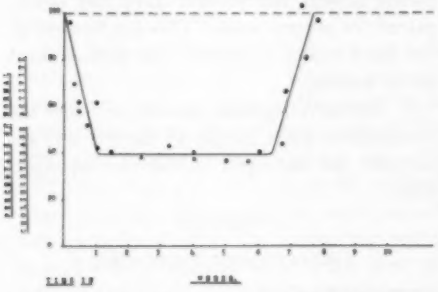

Fig. 4 (de Roetth). Retrobulbar alcohol injection. Average cholinesterase activity (expressed in percentage of normal) of the irises and ciliary bodies of 20 rabbit eyes following the retrobulbar injection of 0.3 ml. of 95-percent alcohol.

Pupillograms were taken on three eyes before and after alcohol injection. At stated intervals the animals were killed, the eyes enucleated, and the cholinesterase content of the iris and ciliary body determined as already noted, the enzyme activity of the injected eye being expressed as the percentage of the normal control eye.

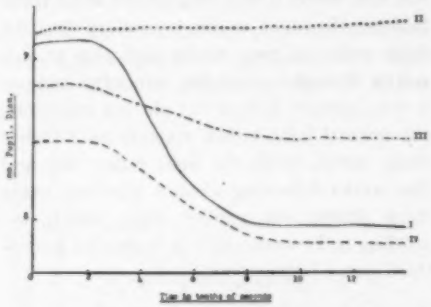

Fig. 5 (de Roetth). Averaged pupillary diameters of three rabbits. (I) Before alcohol injection. (II) Two days after the retrobulbar injection of 0.3 ml. of 95-percent alcohol. (III) One week after injection. (IV) Two weeks after injection.

Results

Clinically the injected eyes all presented the same typical picture, previously described by Kornblueth;[14] there was marked conjunctival edema, congestion lasting about two days; the pupils were large, fixed, and did not react to light; the cornea was anesthetic; after seven to eight weeks, the corneal sensitivity and the pupillary light reflex returned to normal.

Figure 4 demonstrates that the cholinesterase activity decreases rapidly following retrobulbar alcohol injection; at seven days it is about 40 percent of normal and it seems to remain at this level for six to seven weeks, returning to normal by the end of the eighth week.

The first pupillograms (fig. 5) were taken only two days after alcohol injection, because until then there was too much irritation and conjunctival edema. At this time the light reflex was absent in all three animals; it began to reappear after one week, and at two and five weeks it was measurable in all three rabbits. However, it can be noticed that the light reflex at two weeks and also at five weeks, though measurable, is not the same as it was initially before the alcohol injection; the normal light reflex appears as a rather steep curve, while the light reflex two and five weeks following alcohol injection has a more drawn out, gentler slope, which, according to Lowenstein,[15] is typical of partial third nerve impairment.

Discussion

This loss in cholinesterase activity after retrobulbar alcohol injection could be explained in the following manner:

The injected alcohol temporarily and partially paralyzes the ciliary ganglion, which in turn causes a partial and temporary degeneration of the nerves of the iris and ciliary body, since the parasympathetic nerve supply of these tissues comes from the ciliary ganglion. It can then be readily seen that the decrease in cholinesterase activity is due to nerve degeneration.

The remaining 40 percent of the enzyme activity can be attributed mainly to the cholinesterase present in the postsynaptic membrane. The postsynaptic membrane—the myel part of the myoneural junction—plus the sarcolemmal sheath covering the muscle fibers together are responsible for the remaining 40 percent of enzyme activity. Couteaux and Nachmansohn[16] reported similar results, using degenerated muscles in other parts of the body.

The normal pupillary response elicited following psychosensory stimuli means that the sympathetic pathway to the iris was not injured appreciably by the alcohol injection; this would indicate that in the rabbit the sympathetic nerve supply of the iris does not pass through the ciliary ganglion or possibly only some of the sympathetic fibers go through the ciliary ganglion, and others by pass it.

Summary

1. When alcohol is injected into the orbits of normal rabbits, the cholinesterase activity in the iris and ciliary body drops to 40 percent of normal and remains there for several weeks.

2. The drop in enzyme activity is due to degeneration of the parasympathetic nerve fibers in these tissues; this nerve degeneration is in turn caused by the paralytic action of alcohol on the ciliary ganglion.

3. The remaining enzyme activity can be attributed mainly to the cholinesterase in the postsynaptic membrane.

4. Careful, quantitative pupillographic studies demonstrate that following alcohol injection the pupillary light reflex is completely absent for several days and is impaired for several weeks. This impairment of the light reflex is typical for partial third nerve lesions.

5. The pupillograms also showed that the sympathetic nerve supply of the iris was apparently not damaged by the alcohol injection.

Part III

Ciliary ganglionectomy

Introduction

In Part II of this report, it was demonstrated that paralysis of the ciliary ganglion by retrobulbar alcohol injection caused a drop in the cholinesterase content of the iris and ciliary body. Several objections can be raised to this experimental procedure.

Alcohol injection is a crude and inaccurate method of blocking the ciliary ganglion, because the exact location of the tip of the needle can only be estimated and therefore one does not know the amount of alcohol that actually reaches the ganglion.

Also, in the rabbit the iris and ciliary body cannot be separated, therefore it is not

known what the drop in enzyme activity amounts to in each tissue.

To circumvent these difficulties it was decided to attempt surgical ciliary ganglionectomy, and the cat was chosen as the experimental animal, partly because one can separate its iris from the ciliary body, and partly because it is known that in the cat the sympathetic nerve supply does not pass through the ciliary ganglion; thus extirpation of this ganglion in the cat will only be a parasympathectomy, not a sympathectomy. It was for this reason that the following experiment was undertaken.

Method

Experimental surgical excision of the ciliary ganglion is not a new procedure. It was first reported in 1886 by Jegorow[17,18] who described the technique adequately. Since then it has been mentioned several times in the literature, notably by Anderson,[19] Shen and Cannon,[20] Keil and Root,[21] and, recently, by Neidle.[22,23]

The technique is essentially the same as described by Jegorow.[17,18] Under intraperitoneal nembutal anesthesia, the ganglion is approached from the temporal side of the orbit; all cats were operated on one side only, the other side serving as the control. Pupillographic measurements were carried out on several cats; the nictitating membranes of these animals were removed to obtain better exposure for pupillographic studies.

At stated intervals, 18 of these operated animals were killed, and the cholinesterase activity of the irises and ciliary bodies were determined in the usual manner, the enzyme activity being expressed in percentage of the normal control.

Results

Figure 6 demonstrates that the cholinesterase activity in the iris and ciliary body of the cat decreases rapidly following ciliary ganglionectomy; by the end of the third week it drops to 40 percent in both tissues, and remains at this level for many months. Clinically one can notice corneal anesthesia and a large fixed pupil. Pupillographic studies demonstrated complete absence of the pupillary light reflex, both shortly after and also several months following operation.

Discussion

Both the chemical and pupillographic findings following ciliary ganglionectomy agree closely with the results of the retrobulbar

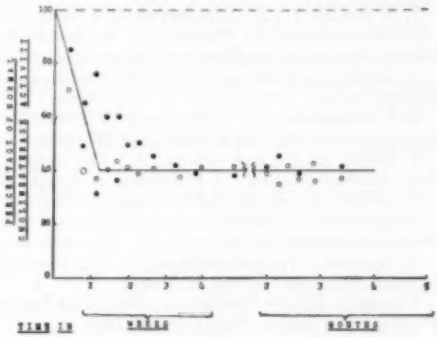

Fig. 6 (de Roetth). Ciliary ganglionectomy. Average cholinesterase activity (expressed in percentage of normal) in the irises and ciliary bodies of 18 cat eyes, following the surgical excision of the ciliary ganglion. The open circles represent the ciliary bodies and the solid circles, the irises.

alcohol injection. However, while the drop in enzyme activity and the impairment of the light reflex are only temporary following the alcohol injection, they apparently are of a permanent nature after surgical excision of the ganglion.

This would indicate that "chemical" ganglionectomy—that is, retrobulbar alcohol injection—differs only in degree from the surgical ganglionectomy. The experimental procedures herein described indicate that retrobulbar alcohol injection, though seemingly a crude and rather inaccurate procedure, is an effective method of blocking the action of the ciliary ganglion, thus causing a partial and temporary parasympathetic denervation of the iris and ciliary body.

Summary

1. Following surgical excision of the cili-

ary ganglion in the cat, the cholinesterase activity of the iris and ciliary body decreased rapidly to about 40 percent of normal, and remained at this low level apparently indefinitely.

2. Pupillographic studies carried out on these animals showed complete absence of the pupillary light reflex.

3. These findings are in agreement with the results obtained following retrobulbar alcohol injection.

635 West 165th Street (32).

ACKNOWLEDGMENTS

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THE OXIDATION OF LACTIC ACID, PYRUVIC ACID, AND VARIOUS MEMBERS OF THE CITRIC-ACID CYCLE BY BOVINE LENS HOMOGENATES*

LAWRENCE O. ELY, M.D.
Iowa City, Iowa

The oxidation of glucose can be divided into two phases: the anaerobic and the aerobic. In the anaerobic or glycolytic phase, glucose is metabolized to lactic acid. In the aerobic or respiratory phase, pyruvic acid, or its reduction product, lactic acid, is metabolized to carbon dioxide and water. The glycolytic phase of lens metabolism has been stressed by Bellows,[1] who points out that "more than six times as much carbohydrate was converted into lactic acid as was changed to carbon dioxide," by the lens according to data by Kronfeld and Bothmann.

Goddard,[2] however, calls attention to the fact that "the fermentation of one mole of glucose to lactic acid liberates only 54 Cal., while the oxidation of one mole of glucose to CO_2 and H_2O yields 700 Cal."

From these figures one can calculate that approximately 68 percent of the known energy available to the lens is derived from respiration, although glycolysis utilizes six times as much carbohydrate as does respiration.

Several workers, using both direct and indirect evidence, have shown that the lens contains the necessary enzymes for the breakdown of glucose to lactic acid.[2-5] The pathways of respiration below the level of pyruvate have been investigated only cursorily in the lens.[1] The lens contains significant amounts of glutathione[6] and ascorbic acid.[7] Von Euler and Gunther postulated that glutathione and ascorbic acid might function in the lens similar to the flavoproteins and the cytochrome system in other tissues.[8] No direct evidence has been offered to verify this postulation.

The proven pathways of biologic oxidation and reduction of pyruvic acid have not been investigated in the lens. In a review of this subject, Stern[9] lists 16 different pathways for the utilization of pyruvate. One of these is through the citric-acid cycle, which is said by Long[10] to represent the main pathway of oxidation in tissues. Krebs[11] has pointed out the significance of the citric acid or tricarboxylic-acid cycle in the oxidation of pyruvic acid.

The present concept of the sequence of this cycle is shown in Figure 1. This metabolic pathway makes available to the tissue the large amounts of energy which are available in pyruvic acid. In one complete turn of this cycle, one molecule of pyruvic acid is oxidized to carbon dioxide and water, and one molecule of oxaloacetic acid is regenerated. The citric-acid cycle forms a common metabolic pathway for proteins, carbohydrates, and fats.

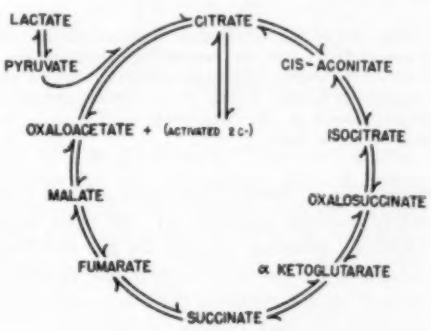

Fig. 1 (Ely). Present concept of the sequence of the tricarboxylic-acid cycle.

The lens is rich in both pyruvic acid[8] and its reduction product, lactic acid.[12] Thus it

* From the Departments of Surgery, Physiology, and Ophthalmology, University Hospitals. This work was supported in part by a grant from The John and Mary R. Markle Foundation.

contains ample quantities of pyruvate for oxidation. The citric-acid cycle has been identified as playing an important role in the oxidation of pyruvate in many other tissues. Because of the significance of the presence of this cycle, it is essential to establish its presence or absence in lens metabolism.

The following investigation is designed to determine if bovine lens homogenates can utilize various members of the citric acid cycle. By showing whether or not the lens is able to oxidize these substrates, one will be able to determine if the citric-acid cycle may be associated with lens metabolism.

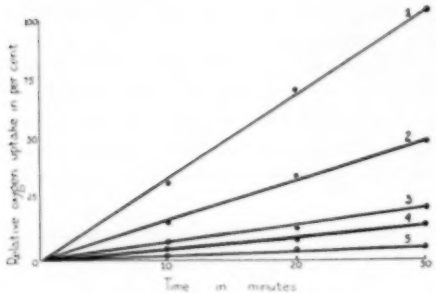

Fig. 2 (Ely). Oxidative decarboxylation of α-ketoglutaric acid by bovine lens homogenates. Curve 1 represents the complete system; Curve 2, no magnesium added; Curve 3, no adenosinetriphosphate; Curve 4, no cytochrome-C; Curve 5, no α-ketoglutaric acid.

Methods

Young bovine lenses were used in this investigation.* The wet weights of the lenses ranged from 1.016 gm. to 1.843 gm. A typical experiment is described in detail.

A group of 10 lenses were weighed, and a homogenate was prepared by grinding them with washed sand in a mortar and pestle. The total weight of each group of 10 lenses was 14.01 gm., with a standard deviation of 0.26 gm. Sufficient M/75 phosphate buffer, pH 7.33[13] was added to bring the total volume to 20 ml. during the process of grinding.

This viscid solution was centrifuged three to four minutes at a slow speed. Sufficient supernatant was available to furnish two ml. of homogenate for each of nine tubes. The centrifugate was tested for activity. This activity was negligible.

The Thunberg methylene-blue technique was used to determine if the homogenate would oxidize lactic acid, pyruvic acid, and various members of the citric-acid cycle. In this technique, under anaerobic conditions, any hydrogen ions mobilized will be utilized in reducing the methylene blue to colorless leukomethylene blue.

In each of six Thunberg tubes were placed 1.0 ml. 1:20,000 methylene blue, 2.0 ml. of M/200 substrate, 1.0 ml. of M/75 phosphate buffer, pH 7.33 (finale concentration of buffer being about M/300), 0.5 ml. of 0.06 M. $MgCl_2$, 0.5 ml. adenosinetriphosphate,* and 2.0 ml. of lens homogenate into the side arm. Three reference tubes were made up in plain test tubes containing only 75, 50, and 25 percent of the usual methylene blue.

The Thunberg tubes were evacuated for five minutes by means of a water pump with constant shaking. (The pressure must be kept low or the homogenate will be sucked out of the tube because of its high viscosity and content of air.) The tubes were all placed in a water bath at 38°C.

The length of time necessary for 50-percent reduction of the methylene blue was determined visually by comparison with the reference tubes. Visual readings were necessary because the resultant homogenate was so turbid that photoelectric readings were impossible. In the absence of substrate there was less than 25-percent reduction during a 30 minutes' observation period.

The methylene-blue technique measures the hydrogen ions made available by oxidation but gives no indication of the source.

* The bovine eyes were donated generously by the Wilson Packing Company, Cedar Rapids, Iowa.

* The adenosinetriphosphate was furnished by Dr. W. A. Robbie and Dr. R. W. Featherstone.

These ions may be obtained from flavoproteins as well as from dehydrogenases. At any given moment several enzymatic reactions may be taking place, and all of these reactions may be supplying hydrogen ions to the methylene blue.

In order to verify the results obtained by the Thunberg technique, the oxidative decarboxylation of α-ketoglutaric acid was determined by the procedure described by Ochoa.[14]

A homogenate was prepared by the method previously described. In each Warburg flask (volume 15 to 16 ml., and constants ranging from 1.2 to 1.4) were placed 2.0 ml. of lens homogenate, 0.1 ml. of 0.12 M. $MgCl_2$, 0.4 ml. M/75 phosphate buffer, pH 7.33, 0.1 ml. of a cytochrome-C preparation assaying 485 gamma per ml., 0.1 ml. of 0.0125 M. adenosinetriphosphate, and 0.2 ml. of 0.75 M. sodium malonate; 0.1 ml. of M/50 α-ketoglutaric acid was placed in the sidearm.*

The total volume was 3.0 ml.; air was used in the manometers, and the temperature of the water bath was 38°C. The manometers were equilibrated for 10 minutes, adjusted, closed, and the contents of the sidebulbs dumped into the flasks.

The oxygen consumption was measured for the succeeding 60 minutes. The oxygen consumption is small, averaging 25-mm. change in the manometers during an hour's time. However, the uptake is linear and can be duplicated in succeeding experiments.

Ochoa has shown that phosphate radicals, magnesium ions, and adenosinetriphosphate are essential for the oxidation of α-ketoglutarate to succinate. Malonate is used to block the succinic dehydrogenase so that the oxidation does not proceed beyond the succinate stage.

Results

In Table 1 are tabulated the data obtained by measuring the dehydrogenase activity by the Thunberg technique. The rate of decolorization of the methylene blue decreased rapidly after 15 minutes, and no activity could be discerned after 30 minutes. A blank containing the entire system except substrate was run with each experiment. In all cases there was less than 25-percent reduction of the methylene blue during a 30 minutes' observation period.

TABLE 1

ANAEROBIC DEHYDROGENATION OF LACTIC ACID, PYRUVIC ACID AND VARIOUS MEMBERS OF THE CITRIC-ACID CYCLE BY BOVINE LENS HOMOGENATES

Substrate	Number of Lenses	Minutes for 50% Reduction of M.B.	Standard Deviation
Lactic acid	24	10.7	3.4
Pyruvic acid	18	16.7	1.66
Oxaloacetic acid	12	13.2	1.54
Citric acid	24	18.6	2.78
α-Ketoglutaric acid	12	15.7	1.48
Succinic acid	30	22.0	2.58
Malic acid	24	17.6	2.16
Control, without substrate	18	<25% reduction in 30 min.	

It should be noted that there is dehydrogenase activity in the bovine lens for all of the acids in the citric acid cycle which were tested. This activity is small indeed, but this result is to be expected because of the low oxygen uptake of the lens.[13] The oxidation of oxaloacetic acid proceeded at a slightly faster rate than did the oxidation of pyruvic acid, indicating that the rate of oxidation of pyruvic acid was not being measured exclusively when the oxaloacetic was being tested. The difference in the rates of oxidation of these two substrates was statistically significant.

* Dr. George Kalnitsky kindly supplied both the α-ketoglutarate and oxaloacetate.

Because of the difficulty in judging the amount of methylene blue reduced and in order to verify the findings in Table 1, the oxidative decarboxylation of α-ketoglutarate was determined by the methods previously described. The oxygen uptake measured by the Warburg technique is expressed in terms of the oxygen uptake for 30 minutes by the complete system. This value is defined arbitrarily as 100 percent and represents a corrected rate of consumption of 32 to 36 c.mm. of oxygen per hour per flask.

The relationship of the various components of this system to maximal respiration is shown in Figure 2. The differences in rates of oxygen uptake between Curve 1 and each of the remaining curves are statistically significant. However, there are no statistical differences among each of the other curves in the figure.

Discussion

The foregoing results demonstrate that the citric-acid or tricarboxylic-acid cycle may have a role in lens metabolism. Additional support for this possibility is given by Krause,[16] who found both citric and malic acids in the lens. The activity of the lens homogenates is small, correlating with the low oxygen uptake of the lens. It is of note that the addition of cytochrome-C was essential for the maximal aerobic oxidation of α-ketoglutarate.

Herrmann and Moses[17] found a similar situation when testing the cytochrome oxidase activity of bovine lenses. Ochoa[14] states that cytochrome-C is a physiologic hydrogen (electron) carrier between α-ketoglutarate and molecular oxygen. If this is true, then one would anticipate the possible isolation of cytochrome-C from the lens.

Conclusions

1. Bovine lens homogenates are capable of oxidizing lactic, pyruvic, oxaloacetic, citric, α-ketoglutaric, and malic acids.

2. The addition of cytochrome-C is essential for maximal aerobic oxidation of α-ketoglutarate by bovine lens homogenates.

University Hospitals.

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SIGNIFICANCE OF CHANGES IN POTASSIUM AND SODIUM CONTENT OF THE LENS*

A MECHANISM FOR LENTICULAR INTUMESCENCE

JOHN E. HARRIS, M.D., AND LETA B. GEHRSITZ, M.S.
Portland, Oregon

Cellular structures, including the lens, have a high potassium and a low sodium concentration. Yet, studies with radioactive cations have indicated that both sodium and potassium traverse the membranes of most cells, normally.[1-4] To account for the maintenance of the normal cation distribution between intra- and extracellular water, the concept of active transfer of sodium, at least, has been developed.[5] This active transfer requires work on the part of the cell, and, thus, is dependent upon its metabolic activity. The uptake of radioactive sodium by the lens[6,7] suggests that an active transport may be present at lenticular barriers as well.

The importance of a normal metabolism in the maintenance of the cation distribution has been amply demonstrated in certain cells. The erythrocyte is of particular interest, because its metabolic intensity is normally low and similar, in some respects, to that of the lens. Various conditions which lower metabolic activity such as reduced temperature,[8] incubation with various metabolic poisons,[9,10] or lack of glucose,[11] cause the erythrocyte to lose potassium and gain sodium. The cation content of the muscle cell also has been shown to vary with its activity and with other influences.[12] Indeed, the readiness with which potassium may move from the intra- to the extracellular phase and sodium in the reverse direction has assumed considerable clinical importance in the evaluation of fluid and electrolyte imbalance.[13]

When the erythrocyte becomes freely permeable to cations and anions in the absence of a compensatory active transfer, it tends to swell and rupture under the influence of a colloid osmotic pressure.[14] Significant to the ophthalmologist is the possibility that a similar force may cause a hydration of the lens. An alteration of the cation content toward equilibration with extralenticular fluid and a lowering of metabolic activity are seen in developing cataract.[15] The failure of a metabolic control of cation distribution may well be a major factor in the intumescence of the lens. Accordingly, we have undertaken a study of metabolic and other influences on the cation and water content of the lens.

METHODS

Rabbit lenses were used throughout. For the most part they were taken from animals used in the Friedman test for pregnancy. The lenses from a single animal served as an experimental situation. As a control, one lens was placed in Tyrode's solution, the other in Tyrode's solution modified in its preparation to produce the effect being studied.

The osmotic pressure of the solutions was kept constant by adding or deleting sodium chloride in the modified Tyrode's. As an aid to bacteriostasis, penicillin sufficient to make a concentration of 5.0 units/ml. was added on the day of use. All solutions were adjusted to the physiologic pH range.

The eyes were enucleated immediately after the death of the animals and the lenses were extracted as soon afterward as was practicable, in any case within one and one-half hours. Although absolute sterility was not obtained, every effort was made to avoid gross contamination. The only major break in sterility occurred in enucleation. The enucleated eye was dropped in sterile saline and thereafter only sterile instruments and solutions were used.

* From the Department of Ophthalmology, University of Oregon Medical School. Part of a study supported by the Argosy Fund and the Smith, Kline, and French Laboratories.

The lens was removed by either an anterior or a posterior approach. In our hands, the posterior approach seemed less traumatic. The lens was placed in a 50 ml. Erlenmeyer flask containing 15 ml. of Tryode's or modified Tyrode's solution. The flask was stoppered with a rubber stopper and placed in a water bath maintained at 38°C. or at refrigerator temperatures. After a specified time the lens was removed.

Those lenses which showed a major shift in cation content were swollen and had a variable amount of fluid under the anterior capsule. This was not observed in the control lens. Since this fluid was considered to represent extracellular water, it was removed by puncturing the capsule with a sharp knife and blotting the lens lightly on a piece of gauze.

The wet lens was then weighed rapidly and dried to constant weight (48 hr.) at 105°C. After being weighed, the dried lens was ashed at 480°C. with the aid of a small amount of sulfuric acid.

The Perkin-Elmer flamephotometer with the internal standard was used to determine the sodium and potassium content of each lens. Results are presented as the difference in concentration, expressed as milliequivalents per 1,000 gm. of water, between the experimental and the control lens.

Comparison of cation and water content

Several pairs of lenses were analyzed to determine how well the sodium, potassium, and water concentrations of the lenses from the same animal normally agree. The results are given in Table 1. The agreement in the potassium and water contents was excellent; that of the sodium was satisfactory.

The agreement between animals was likewise good for sodium and potassium even though quite a range of lens sizes was analyzed. The water contents agreed with published values and showed the inverse proportion to the size (age) others have reported.[16]

TABLE 1

Comparison of potassium, sodium, and water content of the two lenses from the same animal

	Lens Weight (gm.*)	Percent Water*	Cation Concentration Milliequivalents/1,000 gm. Water	
			Potassium*	Sodium†
Range	0.288–0.520	61.5–66.8	115.3–125.6	22.7–29.6
Mean	—	—	121.1	25.5
S.D.	—	—	2.3	2.3
Difference between lenses from same animal				
Range	0.000–0.006	0.0–0.4	0.0–3.4	0.5–3.6
Mean	0.002	0.14	1.8	2.3
S.D.	0.0015	0.13	1.0	1.2

* 11 Animals.
† 6 animals.

Rupture of the capsule

The lens capsule is freely permeable to electrolytes.[17, 18] In the course of our work, however, it soon became apparent that the integrity of the capsule was essential for the maintenance of the normal cation content of lenses immersed in Tyrode's solution. Therefore, the effect of rupture of the capsule was studied.

With care to avoid injuring the underlying lens, the capsule was cut with a sharp instrument. An incision was made from equator to equator on either the anterior or

posterior surface of the lens. Our results indicated little difference between the two surfaces in this regard. However, it was not possible to control this variable adequately since some of the opposite surface frequently became exposed after incubation for several hours.

The amount of lens surface exposed was also variable. This did not appear to be a factor except when the incision was very small (about three mm.) in length. Results on such small ruptures are not included in the data.

Figure 1 illustrates the results. The extent of the shift in cations was not as great as seen under other conditions. The fact that the exchange was essentially the same

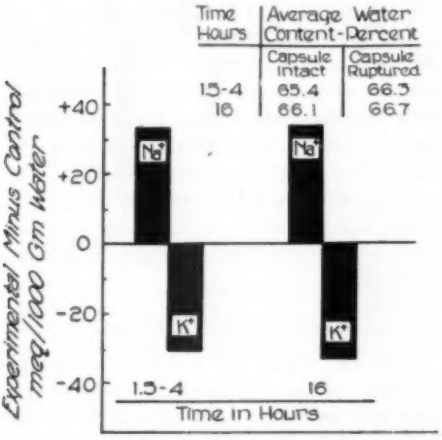

Fig. 1 (Harris and Gehrsitz). Effect of rupture of capsule on cation content of rabbit lenses. Graph represents data from 10 animals.

in four as in 16 hours suggests a rapid attainment of a new steady-state.

Influence of calcium concentration

In many aspects, the calcium ion has a profound effect on the lens. Friedenwald and others[17,18] have observed that it reduces the permeability of the capsule. Weekers[19] reported that calcium is essential for the glycolytic process of the lens. The cataract of parathyroid tetany is too well known to need reference. Swan and Salit[20] demonstrated cataract production in experimental hypocalcemia. The in vitro development of

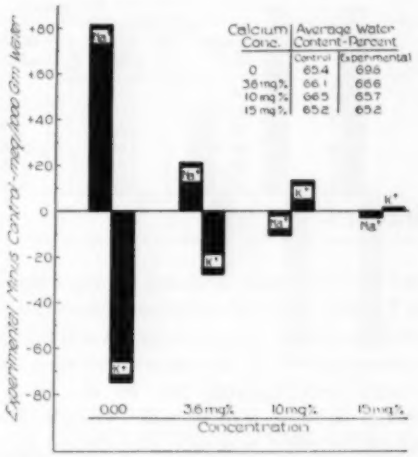

Fig. 2 (Harris and Gehrsitz). Effect of calcium concentration on cation content of rabbit lenses. Graph represents data from 20 animals. Lenses were maintained in solutions for 15 to 20 hours.

lenticular opacities in calcium-deficient solutions has also been reported.[21]

We found that, when calcium was deleted from the Tyrode's solution, a marked loss of potassium and gain of sodium by the lens occurred and the lens became hydrated (fig. 2). The pattern was seen, but to a lesser extent, when the calcium concentration was raised to half that of normal Tyrode's.

On the other hand, a concentration of calcium higher than that of Tyrode's solution, and therefore higher than is normally seen in the aqueous, had a definite protective action. Thus, the lens incubated for some hours in Tyrode's with 10 mg.-percent calcium had a higher potassium and lower sodium and water content than its mate incubated in normal Tyrode's (with 7.2 mg.-percent calcium).

This difference may be ascribed to the fact that there was usually a small but perceptible loss of potassium and gain of sodium

TABLE 2

EFFECT OF LACK OF Mg^{++} ON THE CATION CONTENT OF THE RABBIT LENS

Percent Water		Cation Concentration Milliequivalents per 1,000 gm. of Water					
		Potassium		Sodium		Difference	
With Mg^{++}	Without Mg^{++}	With Mg^{++}	Without Mg^{++}	With Mg^{++}	Without Mg^{++}	K^+	Na^+
63.3	65.3	73.4	65.2	87.8	95.3	− 8.2	+ 7.5
61.6	65.0	110.0	46.0	30.0	109.0	−64.0	+79.0
65.7	65.8	120.0	108.0	36.9	42.2	−12.0	+ 5.3
66.6	66.6	108.2	113.3	41.3	40.1	+ 5.1	− 1.2
67.7	68.5	101.5	91.0	54.6	65.7	−10.5	+11.1
65.3	65.3	119.2	114.1	27.7	33.0	− 5.1	+ 5.3
Mean 64.9	65.6					−15.8	+17.8

and water in lenses incubated for some hours in Tyrode's. The higher calcium concentration protects against this exchange. In still higher concentrations (15 mg.-percent calcium) the results were variable but, on the whole, similar to those with normal Tyrode's. The protective effect was perhaps balanced by a slight toxic action of the higher concentration.

DELETION OF MAGNESIUM

The effect of the deletion of magnesium was so variable that the results are presented in tabular form (table 2). In general, there was a decrease in potassium and an increase in sodium concentration and water content, so that it may be concluded that magnesium is essential to the maintenance of a normal cationic distribution and water content.

The small and somewhat variable changes observed probably attest to the fact that the amount of magnesium normally contained in a lens was sufficient to maintain almost normal activity, even though the lens was bathed in a magnesium-free solution.

Magnesium, in small concentrations, is essential for the activity of many enzyme systems, some of which are undoubtedly present in the lens.

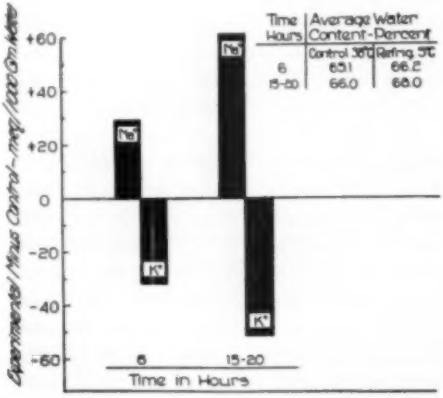

Fig. 3 (Harris and Gehrsitz). Effect of refrigeration at 5°C. on cation content of rabbit lenses. Graph represents data from seven animals.

EFFECT OF REFRIGERATION

One of a pair of lenses immersed in Tyrode's solution was placed in the refrigerator at 5 to 7°C. and the other in the water bath at 38°C. As can be seen from Figure 3, refrigeration of the lens caused a marked drop in potassium and gain in sodium concentration. There was an associated hydration of the lens. Efforts to reverse this change by raising the temperature so far have been unsuccessful.

EFFECT OF VARIOUS METABOLIC POISONS

Studies were made to determine the effect of sodium fluoride on the lens. In effective amounts, the potassium concentration of the lens water fell while the sodium concentration rose (fig. 4). The water content in-

creased considerably. The effect was more pronounced the higher the fluoride concentration and was absent at concentrations of 0.0025 M. Fluoride probably has two effects: (1) The precipitation of calcium and, (2) the blocking of various enzymes in the glycolytic sequence.

Iodoacetic acid blocks the glycolytic sequence at the triosephosphate stage. In the lens (fig. 5) an effective concentration of this acid caused a marked loss of potassium

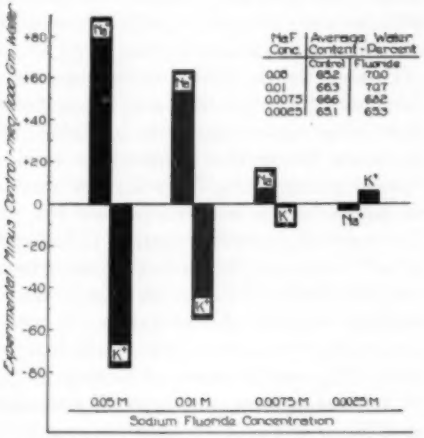

Fig. 4 (Harris and Gehrsitz). Effect of sodium fluoride on cation content of rabbit lenses. Figure gives representative data from seven of 12 animals. Lenses were maintained in solutions for 14.5 to 21 hours.

and gain of sodium and a pronounced hydration.

When the lens was incubated with effective concentrations of sodium cyanide, a moderate exchange of cations took place (fig. 6). Sodium cyanide blocks respiration by combining with iron-containing (and copper-containing) respiratory enzymes. In the concentrations employed and even in higher concentrations a small residual oxygen uptake has been reported.[22]

Replacement of glucose with xylose, fructose, galactose, and pyruvic acid

Glucose is the chief source of nutrition to the lens. Replacing the glucose of Tyrode's solution with the metabolically inert xylose caused a moderate decrease in potassium and gain in sodium concentration (fig. 7). That

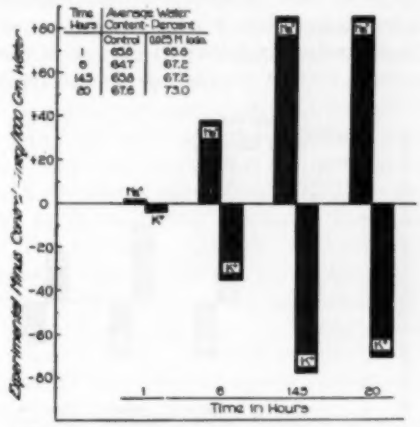

Fig. 5 (Harris and Gehrsitz). Effect of 0.025-M. iodoacetic acid on cation content of rabbit lenses. Graph represents data from five animals.

Conc. NaCN	Average Water Content - Percent	
	Control	Cyanide
0.001 M	64.4	65.0
0.002 M	66.0	67.5

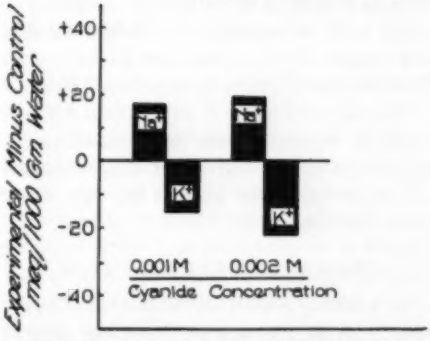

Fig. 6 (Harris and Gehrsitz). Effect of cyanide on cation content of rabbit lenses. Graph represents data from eight animals. Lenses were maintained in solutions for 15 to 20 hours.

the exchange was not greater was perhaps due to the residual glucose and its degradation products in the lens.

This moderate shift in cation distribution

was also seen if fructose or galactose replaced glucose. Weekers[23] observed that neither is capable of preventing the development of an opacity in the isolated lens.

Pyruvic acid occupies a pivotal position in metabolism since it is an end product of the anaerobic breakdown of glucose. It can undergo further reactions of diverse types

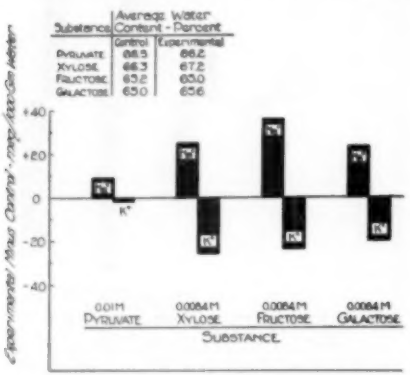

Fig. 7 (Harris and Gehrsitz). Replacement of substrate glucose by various substances. Effect on cation content of rabbit lenses. Graph represents data from 20 animals. Lenses were maintained in solutions for 15 to 20 hours.

such as reduction to lactic acid, oxidation to acetic acid, or oxidation to carbon dioxide and water via the tricarboxylic acid cycle. Pyruvic acid is found in the normal lens.

As seen in Figure 7, it was found effectively to replace glucose in the maintenance of the potassium and water concentrations of the lens although a slight increase in sodium was observed.

Water content of the lens

In general, a shift of cations was associated with an increase in the water content of the lens. Although only slight when the cation shift was moderate, the swelling became marked as the cation concentration approached equilibrium with the extracellular fluid. As mentioned previously, water was frequently observed to accumulate under the capsule of these swollen lenses. Had this been included in our analyses, the changes would have been even greater than reported.

Discussion

Our results leave little doubt that the metabolism of the lens has a considerable influence on its cation and water content. Such diverse means of lowering the metabolism as refrigeration, absence of substrate glucose, absence of magnesium, and poisoning with metabolic posions, all cause a shift in the cation concentration toward equilibration with the extralenticular fluid. Hydration of the lens accompanies this shift.

Conceivably, the shift in cation concentration toward equilibration with extracellular water may result from either a blocking of an active transport mechanism, or an increased permeability, or both. Our results do not distinguish between the two. Nor do they prove that an active transfer of cations* actually occurs at the limiting barrier. However, the blocking of an active transport most logically explains the alteration of cation distribution seen when the metabolism is lowered by refrigeration. Assuming a Q_{10} of 1.4 and figuring the expected exchange at 38°C., from the observed exchange at 5°C. it can be calculated that the metabolism of the lens produces sufficient energy to account for an active transport mechanism. On the other hand, the changes observed when the calcium concentration is reduced are feasibly due solely to an increased permeability of the membrane. The shift observed in 3.2 mg.-percent calcium solution, as contrasted with the protective effect of 10 mg. percent, is best explained on this basis.

Finally, it must be considered that the chemical changes which accompany an altered metabolism may increase the perme-

* An active transfer of both sodium and potassium may not be required. The active transport of sodium alone may account for the maintenance of the cation distribution seen in muscle[8] and erythrocyte.[24] As is the case with other cells, if the lens fiber does contain sodium, the concentration is very low.

ability of the limiting membrane. The effect of iodoacetate and fluoride, in particular, may be the combined one of blocking active transfer and increasing membrane permeability.

The major shift in cation content, including the uptake of sodium, can be considered as taking place within the lens fibers. Thus, the membrane of the lens fiber appears to be the chief barrier to the shift of cations. The reported permeability of the capsule to electrolytes supports this view.

Yet, the intact capsule must have some restraining influence since its rupture is followed by a shift of cations and since subcapsular fluid frequently accumulates. The rapid attainment of a new steady-state indicates that mechanical injury to the epithelium and cortex may occur when the capsule is ruptured. Since oxygen uptake of the lens is increased following rupture of the capsule[25] a Pasteur effect should be considered, as well.

The hydration which accompanies the shift in cation content is due to the colloid osmotic pressure exerted when a system approaches the Donnan equilibrium. Normally, the factors controlling the cation content combine to make the limiting membrane functionally impermeable to salts, so that the normal water content is maintained. With the loss of this functional impermeability, the restraining influence of the extracellular sodium salts is no longer exerted and the lens swells. A concurrent permeability of the membrane to anions is an essential feature of this concept.

The early sequence of events in intumescent cataract formation may be tentatively considered to occur as follows:

Initially, there is a diminution in metabolic intensity or a simple increase in permeability of the lens fiber membrane. Trauma to the capsule may also be an initiating factor. In any event, associated with these changes is a major cation shift which may proceed very slowly.

Hydration follows, due to the colloidal osmotic pressure, and the lens becomes intumescent. Thus, far from being secondary to the formation of a cataract, as has been previously thought, the shift in cation content has a causative relationship to lenticular intumescence. Other factors, such as the hydrolysis of cellular constituents, will contribute to the swelling.

A similar metabolic control of the hydration of the cornea may be postulated. Davson[26] has pointed out that the maintenance of a deturgesced cornea cannot be due solely to an epithelial and endothelial impermeability to sodium chloride. Although this relative impermeability is one essential feature of the system, a superimposed cellular activity must be operative in preventing the corneal swelling. An active transfer of sodium by the epithelium and/or endothelium may well be the missing factor.

Summary

1. The effect of various substances and procedures on the cation and water content of the lens has been studied.

2. The absence of calcium in the incubating fluid, lowering of the temperature by refrigeration, and poisoning by iodoacetic acid and fluoride are all accompanied by a major loss of potassium and gain of sodium and water by the lens fiber, with an accumulation of fluid underneath the capsule.

3. Absence of magnesium from the surrounding fluid, presence of only one-half the normal calcium concentration, rupture of the lens capsule, replacement of glucose with xylose, fructose, or galactose, or poisoning with sodium cyanide cause a more moderate but still quite extensive redistribution of potassium and sodium and gain of water by the lens.

4. Pyruvic acid can replace glucose as the substrate necessary for the maintenance of normal cation and water balance.

5. A higher concentration of calcium (10 mg. percent) than is normally found in the aqueous humor protects the lens from a small

shift in cation and water content which one normally observes in vitro.

6. It is concluded that the hydration of the lens which accompanies the shift of cations is due to the colloidal osmotic pressure of an approaching Donnan equilibrium. This pressure becomes manifest as a swelling when the fiber membrane becomes freely permeable to cations and anions in the absence of a compensatory active transfer.

3181 S.W. Marquam Hill Road (1).

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THE INHIBITION BY THIAMINE CHLORIDE ON THE RETINAL RESPONSES CAUSED BY NICOTINE*

AUSTIN I. FINK, M.D.
Brooklyn, New York

It has been demonstrated that the inhalation of cigarette smoke produces definite alterations (widening) of the normal angioscotoma.[1] This change was attributed to the nicotine in the tobacco, since the inhalation of tobacco of low nicotine content was shown to effect little if any change in the angioscotomas. Pick and Una[2] have recently brought attention to the blockage of the nicotine action on blood pressure by thiazole-compounds (sulfathiazole and thiamine.) It was therefore decided to investigate whether thiamine chloride might inhibit the angioscotomal alterations attributed to nicotine.

METHODS AND MATERIALS

The word "angioscotoma" signifies a "defect in the visual fields related in form to the pattern of distribution of the retinal vessel tree."[3] These shadows (after extensive research) have been interpreted as arising through modifications of the retinal perivascular spaces and in the retinal synaptic junctions.[4]

TECHNIQUE

The scotoma was mapped according to the method advocated by Evans.[5] The defects in the visual fields could thus be studied both qualitatively and quantitatively.

The Evans stereocampimeter and charts were used. Monocular fixation was employed throughout the experiment. The diameter of the spherical, white test object employed was in all cases 0.4 mm. (illumination of the chart was approximately 15 foot-candles). The blindspot of Mariotte was outlined. This was followed by mapping the main superior angioscotoma moving the test object from seeing to the blind area. Care was taken at all times to move the test object at right angles to the border of the defect.

SUBJECTS

A group of five subjects was studied, each on two successive days. The ages of the subjects ranged from 20 to 26 years. All known causes for alteration of the angioscotoma were carefully eliminated. Each subject was found to be in good health.

PROCEDURE

The subjects rested for approximately 10 minutes before any mapping was begun. During this time the pulse was recorded. The subjects were familiarized with the apparatus and instructed to respond to the disappearance of the test object either by tapping with a pencil or by saying "gone."

The first map or control was then plotted. On the first day the subject smoked one cigarette with inhalation. Successive mappings were then plotted in accordance with the procedure established in the original experiments.[1]

The next day the subject was injected subcutaneously with 100 mg. of thiamine chloride. This was followed 20 minutes later by the smoking of the second cigarette. Any alterations in the angioscotoma were again plotted. An interval of 20 minutes was allowed to elapse after injection, before smoking was begun, to permit time for the absorption of thiamine into the tissues.

OBSERVATIONS

The figures and table show the observations made with the subjects. A widening of

* From the Department of Ophthalmology of the Long Island College Hospital and The State University College of Medicine at New York.

the angioscotoma was noted in each subject following the inhalation of one cigarette. However when smoking was preceded by the thiamine injection, two of the subjects demonstrated minimal widening. One showed no change at all from the control study, while the remaining two demonstrated a decrease in the area of scotoma.

In the first series (cigarette alone), the maximum effects were noted in an average of 14 minutes. The increase in scotoma units averaged 28. The effect was lost in an average of 59 minutes (fig. 1).

In the second series (thiamine plus cigarette), the maximum effects were noted in an average of 18 minutes; the increase in scotoma units averaged two. The effect was lost in an average time of 47 minutes (fig. 2).

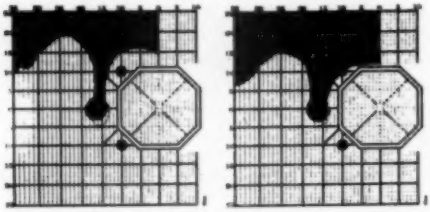


Fig. 1 (Fink). Tobacco without thiamine. Subject J. D. (Control study) 140 scotoma units. (Maximum effect) 188 scotoma units. (25.5-percent increase.)

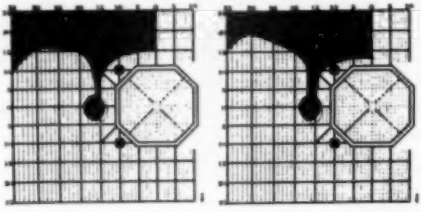


Fig. 2 (Fink). Tobacco with thiamine. Subject J. D. (Control study) 150 scotoma units. (Maximum effect) 143 scotoma units. (4.6-percent decrease.)

Blood pressure changes were not recorded since it had been demonstrated[1] that, under these conditions, alterations were not detectable. Pulse rate changes were noted, and alterations similar to those found in the original studies were observed.

Comment

The striking observation in this study was that in each of the five subjects tested there was a definite decrease in the alteration of the angioscotoma when the smoking of one cigarette was preceded by the injection (subcutaneously) of 100 mg. of thiamine chloride. An apparent decrease in the area of scotoma, when compared with the control study, was noted in two subjects.

As stated in the introduction of this paper, angioscotoma alterations following the inhalation of cigarette smoke have been attributed to the nicotine content of the tobacco. Smoking cigarettes of low nicotine values was shown to effect little if any change in the angioscotomas.[1]

TABLE 1

Appearance and duration of changes in the scotoma

Subject	First Change	Maximum Effect	Effect Lost	Scotoma Unit Changes
J. D.				
(a)*	5 min.	5 min.	85 min.	+25.5%
(b)†	5 min.	30 min.	100 min.	− 4.6%
D. C.				
(a)	3 min.	15 min.	85 min.	+12.8%
(b)	20 min.	20 min.	60 min.	+ 1.9%
P.B.				
(a)	13 min.	23 min.	58 min.	+17.7%
(b)	0 min.	0 min.	0 min.	− 0.0%
N. H.				
(a)	2 min.	5 min.	60 min.	+15.2%
(b)	2 min.	15 min.	30 min.	−23.0%
R. S.				
(a)	5 min.	14 min.	59 min.	+13.0%
(b)	7 min.	25 min.	47 min.	+ 6.3%
Average				
(a)	4 min.	14 min.	59 min.	+16.8%
(b)	7 min.	18 min.	47 min.	−11.6%

* (a) Tobacco alone.
† (b) Tobacco plus thiamine.

Nicotine exerts its effect in small doses (as employed in this study) through a stimulation of the sympathetic ganglia.[6] Adrenalin is thus liberated with a consequent vasoconstriction and rise in blood pressure.

Thiamine chloride has been shown to play an important role in maintaining the resting potential of the nerve.[7] It has also been

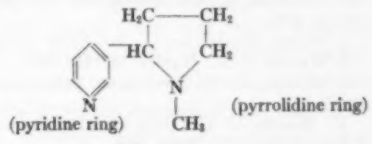
found that this vitamin, which is produced in considerable quantity during nervous activity, acts as a moderator or inhibitor of overstimulated sympathetic synapses.[8] Since the action of nicotine occurs through a stimulation of the sympathetic ganglia, one might then assume that the stimulation of sympathetic synapses by nicotine might be facilitated in the presence of a deficiency of thiamine in the central or peripheral nervous system.

The theory of biologic competition between two chemicals which have certain similarities in molecular structure is well recognized.[9] A classical example of the theory is found in the competitive antagonism between para-amino-benzoic acid (found essential for the metabolism of several microorganisms[11]) and sulfanilamide[10]—para-amino-benezene sulfonamide—(well recognized for its chemotherapeutic properties):

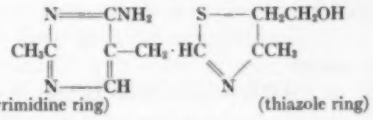
p-Amino-benzoic acid Sulfanilamide

This fundamental concept is carried through by Pick and Una[2] and offered as a possible basis for the inhibition of nicotine by thiamine. To go further, the nicotine molecule is composed of a pyridine and a pyrrolidine ring. The thiamine molecule contains a thiazole and a pyrimidine nucleus. The inhibitory effect of thiamine on nicotine is ascribed to "a competitive action between the pyridine ring of nicotine and the thiazole nucleus of thiamine."[2]

However, on the basis of structural similarity, one might be inclined to think of an antagonism between the pyrrolidine nucleus of the nicotine and the thiazole ring of thiamine. Structural similarities can be observed in the following diagrams:



NICOTINE



THIAMINE

The vitamin is thought to secure the enzymatic balance necessary for the undisturbed function of the ganglia. This in turn alters the stimulation in or on the synapse by nicotine, since the latter molecule is neither destroyed nor altered in the process.[2]

Conclusions

Under the conditions of this study and in the subjects tested the following conclusions were drawn:

1. The subcutaneous injection of 100 mg. of thiamine chloride prior to the smoking of one cigarette with inhalation contributed to the inhibition of the angioscotomal alterations found when a cigarette was smoked without previous injection.

2. Inhibition by thiamine on the nicotine molecule has been attributed to competitive antagonism between structurally similar molecular rings.

3. Thiamine acts as a moderator of overstimulated sympathetic synapses; the point at which stimulation by nicotine takes place.

110 Remsen Street (2).

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THE INFLUENCE OF DONOR-RECIPIENT SENSITIZATION ON CORNEAL GRAFTS*

A. Edward Maumenee, M.D.
San Francisco, California

The clouding of mechanically successful corneal grafts three to five weeks postoperatively has not been explained adequately in eyes which would be expected to support a clear transplant. Many suggestions have been offered to account for this abnormality of the graft, but none have been substantiated sufficiently by animal experimentation or clinical observation.

It is the purpose of this report to present experimental evidence which will support the theory that one cause of late clouding of corneal grafts is the sensitization of the recipient to material from the donor, and that this type of reaction is dependent on the biologic specificity of individual animals of the same species. A possible method of preventing this type of clouding is also mentioned.

No attempt will be made to refer to all of the suggestions which have been put forward as a cause of the late clouding of corneal grafts. Only a few of the more recent reviews will be cited.

In a symposium on corneal transplants in 1947, Castroviejo[1] stated that the late clouding of keratoplasties was due to a uveitis in the recipient eye and that removal of a focus of infection sometimes would result in a clearing of the graft. At the same symposium,[2] a second suggestion was that this type of opacification was due to an allergic reaction which resulted from a sensitization of the recipient by the homotransplanted material. No experimental data were offered to substantiate this view.

In 1948, Paufique, Sourdille, and Offret[3] divided the cases with technically perfect corneal grafts which became cloudy into three groups according to the time of onset of the opacification. The suggested cause for each of these types of clouding was based on clinical observation.

The first group included those eyes in which the disturbance began by the 10th postoperative day. The etiologic factor in these instances was the sensitization of the recipient by foreign protein in the transplant.

A second group included those cases in which the opacification occurred during the third postoperative week. The clouding of these grafts was caused by a disturbance in the metabolism of the transplant.

The third group included those cases in which the graft became cloudy after the

* From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine. This investigation was supported by a research grant from the National Institutes of Health, Public Health Service.

third postoperative week. This type of opacification was due to an invasion of fibroblasts and blood vessels from the recipient cornea.

Klima,[4] in 1949, stated that the clouding of corneal transplants was due to an allergic reaction caused by the immunobiologic difference between the host and the donor. He based his opinion on a series of experiments in which he produced a keratitis in rabbits by two injections, given 14 days apart, of 0.05 cc. of homogeneous corneal extract. Corneal inflammation occurred frequently if the material for the two injections came from the same donor, but occurred only rarely if a separate donor was used for each injection. He thought this demonstrated that a sensitization of the recipient to the donor could be produced by material in a corneal transplant.

The only reference to late clouding of grafts in the International Symposium on Corneal Surgery in 1949 was that of Barraquer[5] who stated that this type of opacification was due to a "hypotrophic" change because the graft "may not receive a sufficient quantity of the elements necessary for its metabolism. . . ."

Status of donor-recipient sensitization in tissues other than cornea

If skin is transplanted from one individual to another, it will "take," survive, and show signs of proliferation in the form of migration and mitosis of the epithelial cells. Almost invariably, however, the grafts become necrotic and slough two to six weeks after operation. This destruction of the transplanted material is the result of a sensitization of the recipient by some product of the donor graft.

Underwood,[6] in 1914, on the basis of clinical observation on a patient who had skin homotransplants for extensive burns, suggested that the destruction of the donor material was similar to an anaphylactic reaction. Holman[7] made a similar observation on a child who had had an avulsion of the skin of the leg and developed an exfoliative dermatitis after receiving multiple skin grafts. He also noted that the sensitization produced by the grafts was specific for an individual donor. The skin taken from a second donor remained in excellent condition for four to five days after a second set of grafts from the original donor had completely disintegrated. This occurred even though the second set of grafts from the original donor had been applied several days after those from the second donor.

Medawar[8] in a series of experiments on rabbits has added further evidence to the theory that homografts are destroyed because of donor-recipient sensitization. He has shown that multiple skin grafts are destroyed more rapidly than a single pinch graft, and that a second set of transplants from the same donor disintegrates more rapidly than the original material, even though they are inserted at a point distant from the original operative site.

Skin taken from a second donor and inserted in the original operative site survives for as long as the first set of grafts. The allergic reaction appears to be dependent on a vascular invasion of the donor material.

Grafts to the anterior chamber survive for a much longer time if they remain free in the aqueous or attached to the avascular posterior surface of the cornea than if they adhere to the anterior surface of the iris and become vascularized.

Donor-recipient sensitization is not organ specific, however, for the accelerated destruction of homografted skin can be produced by previous injections of leukocytes. The sensitized state cannot be demonstrated by tests for agglutinins in the blood, nor can it be elicited by the use of tissue cultures and serum from the sensitized animal.

These observations and many others have adequately demonstrated that almost any tissue transplanted from one individual to another will be destroyed due to the results of sensitization of the recipient to the donor material.

There are instances, however, in which tissue can be transplanted from one individual to another and appear to survive. These are grafts from one identical twin to another and cartilage grafts. Grafts between identical twins survive because of the biologic similarity of the donor and the recipient. Cartilage transplants are probably not destroyed because there are not enough cells in the material to elicit an allergic reaction and the cells are protected by the cartilaginous matrix from the blood vessels of the recipient.

There are other conditions in which grafts are not destroyed for several weeks or months after transplantation. These are grafts to the anterior chamber of the eye, the uterus (pregnancy), and the brain.

Transplants to the anterior chamber of the eye are not destroyed so rapidly as elsewhere in the body because the blood vessels of the recipient do not invade the donor material for several days to a week, thereby allowing the grafted material to become acclimated to the host.

In pregnancy, the embryo survives in the uterus because of the lack of vascular invasion from the host and because of the weak antigenic properties of the embryo.

It is not known why grafts to the brain survive, but it has been suggested that the absence of lymphatics in the brain prevents tissue transplanted in this area from causing a donor-recipient sensitization.

The status of corneal grafts in relation to donor-recipient sensitization has never been clearly defined. In recent studies[9, 10] which were made to determine the fate of the donor material in corneal grafts to rabbits, it was concluded that the epithelium and endothelium of the transplants were replaced. The corneal nerves degenerated. The stromal fibers and glassy membranes were not replaced. The stromal cells did not undergo a massive dissolution at any time, but it could not be determined whether or not the keratocytes were gradually replaced.

On the basis of these histologic observations, it can be suggested that clear grafts do not show a donor-recipient reaction similar to that found in the skin for there is no massive destruction of stromal cells at any one time after operation. The poor antigenic properties of corneal transplants may be accounted for by the relatively small number of cells in a corneal transplant, and the avascular bed into which it is inserted. In these respects, corneal grafts may be compared to cartilage grafts.

The following studies were designed to show whether or not sensitization of the recipient to the donor material would affect the clarity of a corneal graft.

Experimental studies

Young albino rabbits weighing approximately two to four Kg. were obtained from a single dealer. No attempt was made to determine whether the animals used in a single experiment were from the same litter or were genetically related.

Keratoplasties were performed with a mechanical trephine. Three to four grafts, 4.5 mm. in size, were obtained from one eye of the donor and a single transplant was inserted into an eye of the recipient. Transplants were held in place by criss-cross sutures inserted in the recipient cornea.

The eyes were cleansed every day for the first week after operation and every other day during the second week. The sutures were removed on the seventh postoperative day. The reactions of the eye and the transplant were recorded twice a week.

Grafts which are clear or only slightly edematous two weeks after operation pass through the following sequence of events. The recipient cornea and transplant are edematous during the first seven to 10 days. The iris is hyperemic and thickened.

Blood vessels invade the cornea to a varying degree depending on the extent of the postoperative reaction. They usually advance to the margin of the donor material, and occasionally will invade the edge of the transplant for approximately 0.5 mm.

The anterior chamber is usually present at all times and anterior synechias occur only rarely. The eyes show a slight to moderate inflammatory reaction two weeks after operation, and are almost quiescent at three weeks after the operation (fig. 1).

With this technique, approximately 50 percent of the homotransplants to normal rabbit corneas remained clear. If the transplant was clear or only slightly hazy, the inflammatory reaction mild and the pannus not extensive, two weeks after operation, then only one graft in 60 eyes became cloudy at a later date. This is in marked contrast to human grafts which not infrequently appear successful two weeks after operation only to become cloudy a few weeks later.

A possible explanation for the absence of this type of late clouding in rabbit corneas is that they are not as susceptible to donor-recipient sensitization as man, and that the 4.5-mm. grafts which were used do not supply enough antigen to produce this reaction.

An attempt was therefore made to increase the dose of antigen in these rabbits by inserting a 2.0 by 2.0 cm. piece of skin from the same donor into a pocket flap under the panniculus carnosus of the recipient abdominal wall. It has been shown that skin grafts of this type survive and produce a sensitization as well as those place on a prepared surface bed.[8c]

In the first set of experiments, skin was inserted two weeks before the corneal transplant in 12 animals. This was done to allow the sensitization produced by the skin to have its greatest possible effect on the corneal tissue. Operations done in this manner resulted in opaque grafts in every instance. In several eyes, the donor material became very edematous, appeared necrotic, and sloughed.

In the next set of grafts, the skin and corneal material were inserted at the same time in eight rabbits. Again all of the transplants became cloudy but, in two instances, the grafts were relatively clear at the end of 14 days before they became opaque during the third postoperative week.

These two sets of animals indicated that the donor-recipient sensitization so produced had a deleterious effect on the grafts. However, there are so many uncontrollable variables which might produce an opacification of a corneal graft in rabbits during the first two postoperative weeks that it was thought desirable to perform an experiment in which more exact controls could be obtained.

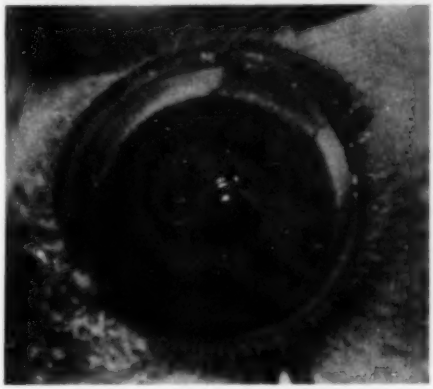

Fig. 1 (Maumenee). Clinical reaction in rabbit eye 10 days after corneal graft.

To this end, the corneal operation was performed first and only those animals which had a clear or only slightly cloudy graft in a relatively uninflamed eye two weeks after the operation were used.

Skin from the same donor which supplied the corneal material was then inserted into the abdominal wall of the recipient, two to four weeks after the ocular operation. Twenty-eight grafts in 30 animals so treated became cloudy two to four weeks after the insertion of the skin transplants. This clouding of the grafts is in striking contrast to the late clouding of only one graft out of 60 animals in which a booster skin graft was not given.

Further control experiments were done to determine whether the deleterious effect of skin transplants on the corneal grafts was due to an organ or an individual specificity.

To this end, in 14 animals, skin from sup-

Fig. 2 (Maumenee). Clear corneal graft two weeks after operation, showing slight edema of the stroma, normal stromal cells, epithelium and endothelium. (×100.)

posedly genetically unrelated donors was inserted two to four weeks after the ocular operation. Twelve grafts remained clear. In eight of these animals, one eye was grafted and two weeks later skin from the donor of the first eye was inserted under the abdomen. At the same time a corneal transplant was inserted into the unoperated eye from an unrelated donor.

In six instances the unrelated cornea remained clear and the related cornea became cloudy. Thus, it seems that the clouding of the corneal transplants produced in these animals by the insertion of skin from the same donor is due to an individual hypersensitivity.

It is not possible to state with any degree of certainty why the two grafts in the sensitized animals did not become opaque. Possible explanations are: (1) That sensitization cannot be established in every animal by this technique, or that not all grafts will be influenced by this sensitization, (2) the donor and recipient animals may have been litter mates, (3) or the graft survived because of the lack of functioning blood vessels in the recipient cornea.

It is interesting that when the corneas of these two animals were examined with the aid of a strong light and a loupe which magnified approximately 1.7 times, blood vessels could not be seen in the recipient cornea for more than a millimeter or two.

The clinical appearance of the ocular reaction in these eyes was extremely consistent. On the day before or on the same day the graft became cloudy, the corneal and circumcorneal vessels became congested, and the iris hyperemic and thickened. The stroma in

Fig. 3 (Maumenee). Corneal graft which was clear for five weeks before opacification due to sensitization. Note edema of stroma, scarcity of stromal cells, and detachment of endothelium.

the graft adjacent to the largest group of vessels became edematous and cloudy.

During the next day or two the clouding spread throughout the entire graft and not infrequently the adjacent recipient cornea became slightly edematous. The blood vessels invaded the graft and, in the most severe reactions, the keratoplasty became opaque and vascularized.

In several instances in which the reaction

Fig. 4 (Maumenee). Corneal graft which was clear for five weeks before opacification due to sensitization. Note edema of stroma, absence of stromal cells and endothelium, and invasion of blood vessels in superficial stroma.

was not so severe, the edema in the keratoplasty subsided leaving either a nebulous opacity in the superficial portion of the transplant or a thin white sheet of tissue on the posterior surface of the graft.

These latter reactions seemed to occur more frequently when the skin was inserted three to four weeks after the corneal graft rather than two weeks after the operative procedure. The course of events in these transplants was extremely similar to that

Fig. 5 (Maumenee). Same eye as shown in Figure 4. Recipient cornea adjacent to corneal graft. Note normal appearance of cornea as compared to graft.

seen in the late clouding of human keratoplasties.

A histologic examination has been done on only eight eyes in which corneal grafts were clear and then became opaque due to an induced allergic reaction. Material for this part of the study is, therefore, not sufficient to give a detailed chronologic description of the sequence of pathologic changes which occur.

Histologic sections of clear grafts two to three weeks postoperatively usually show the transplant to be the same as a normal cornea except for a slight edema of the stroma (fig. 2). There are few, if any, polymorphonuclear cells in the material and the stromal cells are normal in appearance and number.

Corneal transplants which remain clear for four to six weeks after operation before they become cloudy due to a sensitization, show many changes which are not found in clear grafts. In eyes removed two to six days after the onset of the clouding, the stroma of the graft is edematous, and the endothe-

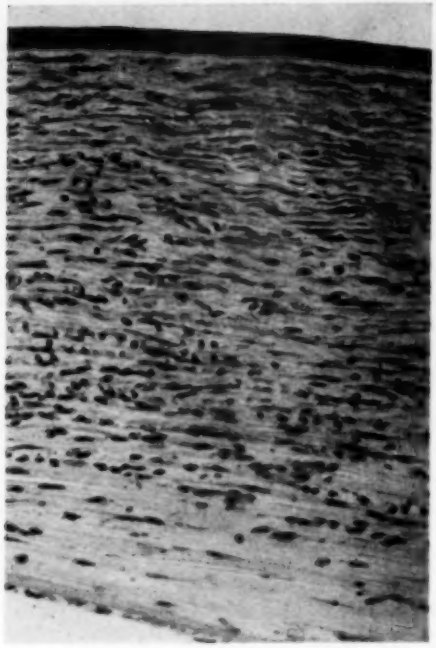

Fig. 6 (Maumenee). Corneal graft which was clear for six weeks before opacification due to sensitization. Note infiltration with leukocytes and increased number of stromal cells.

lium is detached from Descemet's membrane (fig. 3).

In some instances there is an almost complete loss of stromal cells in the transplant (fig. 4). In other grafts there is a marked infiltration by polymorphonuclear and lymphocytic cells (fig. 6). The blood vessels adjacent to and in the transplant are congested and dilated.

In eyes which have been removed a week or so after opacification, the tissue is still infiltrated with polymorphonuclear and lymphocytic cells which are migrating to the graft. The endothelial and stromal cells in the recipient cornea remain normal (fig. 5).

It may be concluded from these experiments that sensitization of the recipient to a specific donor will produce an opacification of the graft if the reaction occurs before the fifth to seventh postoperative week. The histologic response of the donor material is essentially the same as that seen in homogeneous skin grafts.

The severity of the reaction in the eye and the permanency of the opacity is in part dependent on the time of onset of the sensitization after the insertion of the corneal graft. The clinical appearance of the opacification when it occurs three to seven weeks after the ocular operation in rabbits is very similar to the late clouding of corneal grafts in man.

Evidence for Survival of Donor Cells in Grafts

Many attempts have been made to determine whether or not the donor stromal cells in homogeneous grafts survive or if the transplant merely acts as a framework for the recipient cells. This question cannot be definitely answered by routine histologic studies, for it is impossible to determine by this method if there has been a gradual replacement of the stromal cells. Likewise, introduction of some foreign substance into the cells of the recipient or donor to identify them is subject to error, for it is possible that the marked cells may be destroyed and their identifying substance phagocytized by the surviving cells of the host or the donor.

The use of the biologic individuality of the animal would seem to offer a solution to the problems of identifying the donor material. Sufficient studies have not been done as yet to state with certainty whether the individual sensitivity is due to the stromal cells or fibers. However, work on other tissues suggests that it is the cells and not the framework which causes the sensitization.

If this is correct, it appears that the donor cells either survive or maintain their identity for a month or six weeks after grafting and then die or assume the nature of the host. Thus, 28 grafts in 30 instances became cloudy if sensitization was produced before the sixth to seventh postoperative week.

On the other hand, when skin from the same donor as the corneal transplant was inserted into seven animals from six weeks to

four months after the ocular operation, in no instance did opacification of the cornea occur.

It is possible that atrophy and obliteration of the blood vessels in the cornea prevented sufficient antibodies from reaching the graft to cause an allergic reaction in these cases. To test this, one eye was kept in an irritated state and the blood vessels of the conjunctiva engorged, for two months after skin grafting, by injecting hypertonic sodium chloride under the conjunctiva twice a week. The corneal transplant in this animal did not become opaque.

Prevention of opacification of corneal grafts caused by donor-recipient sensitization

The discovery of the response of allergic reactions to cortisone and ACTH[11] suggested that these compounds might be useful in preventing the clouding of corneal grafts which occurs as a result of donor-recipient sensitization. It seemed that these substances might be of value even though they prevented the allergic reaction only during their administration and for a short time thereafter, for it has been shown, in this study, that sensitization after the seventh postoperative week had no influence on the clarity of the corneal grafts.

In six rabbits a keratoplasty was performed and skin from the same donor was inserted at least two weeks later. These animals were treated with intramuscular injections of 15 mg. cortisone per Kg. of body weight each day. This is approximately 15 times the dose used in man.

In three animals the drug was begun after the graft became cloudy as a result of sensitization.

In the first rabbit, skin was inserted three weeks after the corneal operation and the transplant became cloudy and the eye hyperemic 22 days after the skin graft. Cortisone was started on the second day of clouding of the graft and was continued for six days. The hyperemia subsided in two days and the graft cleared to translucency in 11 days. Three weeks after the cortisone was discontinued, and eight weeks after the skin operation, the transplant was clear. Unfortunately, at this time the rabbit died.

In a second animal, skin was inserted 28 days after the ocular surgery and clouding of the graft occurred in 15 days. Cortisone was started and continued for six days. Both the hyperemia of the eye and the graft cleared in four days. The eye has remained unchanged for 8.5 weeks since the cortisone was discontinued and 11.5 weeks since the skin graft.

In the third animal, skin was grafted 32 days after the corneal transplant and the keratoplasty became cloudy 11 days later. Cortisone was started on the second day of the opacification and was continued for nine days. The hyperemia of the eye responded in four days and the graft cleared in nine days. The transplant is still clear and it has been five weeks since cortisone was last used and eight weeks since the skin operation.

In three other animals, a homograft was inserted in one eye and, two weeks later, skin from the same donor was placed under the panniculus carnosus of the abdominal wall and a corneal heterograft from a cat was inserted in the opposite eye. Cortisone, 15 mg. per day, was begun on the eighth day after the last operation and was continued for 14 days.

One rabbit died two days after the cortisone was discontinued. This was 17 days after the skin graft.

A second rabbit died two weeks after the cortisone and five weeks after the skin graft. Again, the grafts in both eyes remained clear throughout the postoperative course.

In the third animal, the heterograft was an operative failure. The homograft, however, remained clear for three weeks after the cortisone was discontinued and six weeks after the skin operation (fig. 7). During the seventh week after skin graft, nine weeks after the keratoplasty, the transplant became slightly hazy and vascularized.

It is realized that cortisone has not been

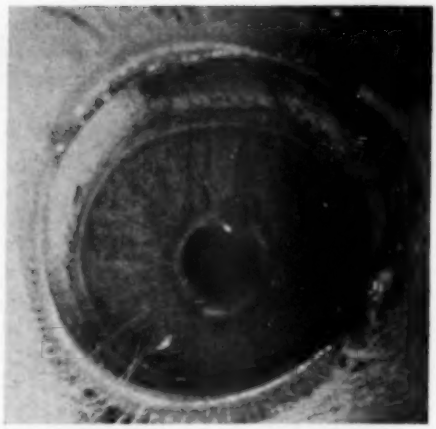

Fig. 7 (Maumenee). Clear corneal transplant six weeks after skin graft. Animal treated with cortisone.

used in enough animals in this experiment to allow definite conclusions to be drawn, but it does seem that this drug has had some beneficial effect on the clouding of corneal grafts which results from a donor-recipient sensitization.

Summary

1. Corneal transplants performed in the manner described in this paper have remained clear in approximately 50 percent of the grafts.

2. Only one graft in 60 instances became cloudy at a later date if the graft was clear or only slightly cloudy two weeks after the corneal operation.

3. When skin from the same donor was used as an antigenic supplement, two weeks after the corneal operation, the corneal transplant became cloudy in 28 out of 30 eyes within two to three weeks after the insertion of the skin.

4. The clinical appearance of the ocular reaction in these eyes was similar to that observed in the late clouding of corneal grafts in man.

5. Histologic sections of the grafts which became cloudy as a result of sensitization in rabbits show an inflammatory reaction similar to that which occurs in homogeneous skin grafts.

6. The biologic individuality of a corneal transplant appears to last for only six to eight weeks after corneal grafting.

7. The opacification of corneal grafts which resulted from a sensitization to the donor material may be influenced by the prophylactic use of cortisone.

Discussion

It is readily admitted that the method used to produce a donor-recipient sensitivity and a clouding of the graft in these experiments differs from a keratoplasty in man in that skin and cornea are never transplanted from the same donor in man. There are two points of similarity, however, in the clouding of the grafts which strongly suggests that it may be of the same origin in both species. First, the clinical appearance of the grafts and the reaction in the eyes are remarkably alike. Second, the time of onset is approximately two to seven weeks after the insertion of the donor material in both cases.

It has been previously stated that one of the reasons why corneal homografts do not always elicit an allergic reaction is that a relatively small number of cells are transplanted to an avascular area. However, it seems reasonable that, if almost every other tissue in the body produces a sensitization when transplanted from one individual to another,[12] corneal transplants would at least occasionally cause a similar response.

Furthermore, the reactions would be more likely to occur if the recipient cornea was heavily vascularized. It has been shown that homografts of skin to the anterior chamber of the eye survive only when they are not in contact with the blood vessels of the iris.[8c]

Clinical studies of corneal transplants are compatible with this suggestion for it has been shown that a higher percentage of grafts will remain clear in patients with keratoconus or central corneal scars where

no blood vessels, or only occluded vessels, are present than if the cornea is heavily vascularized.

It may be asked why a spontaneous sensitization to corneal grafts does not occur in rabbits, if one is expected to believe that this can happen in man. This cannot be answered with certainty at this time, but there are several possible explanations.

First, only normal avascular rabbit corneas were used for recipient eyes. Next, the size of the specimen transferred was small as compared to the rabbit cornea. The grafts were 4.5 mm. in diameter and the cornea 14 to 15 mm. in diameter. In man the grafts are usually 5.5 to 7.0 mm. in diameter as compared with the corneal diameters which are 11 to 12 mm.

Finally, it is possible that rabbits require a larger dose of antigen to produce sensitization than is required in man. This is supported by the findings that nerve grafts survive in rabbits and other lower animals but they are invariably replaced by fibrous tissue in man.[13]

This presentation is not intended to convey the idea that the only cause of clouding of corneal grafts is the sensitization of the recipient to the donor material. There are other obvious causes for clouding of the grafts during the first two postoperative weeks. These are defects in the donor material, poor apposition of the donor-recipient tissues, and pyogenic postoperative infections.

There are also other factors which can cause an opacification of the graft after the second postoperative week. Some of these are well established and others have only a theoretical basis. Thus, it has been observed many times clinically that grafts will become opaque due to an extension of a disease process. This is true in eyes which have an endothelial dystrophy, a lipoidal dystrophy of the stroma, or an active corneal inflammation.

There are also two other possible causes that might account for the late opacification of grafts in some cases. These are foci of lymphocytes in old corneal scars and the destruction of some hypothetical enzymatic system in the cornea or at the limbus which produces a chemical essential for the clarity of the cornea.

It does seem, however, that there are many instances of opacification of grafts where none of the factors just mentioned apply. In this group of cases, it is felt that a donor-recipient sensitization is the genesis of the clouding of grafts.

On the basis of experimental work presented at this time, it seems reasonable that cortisone or ACTH should be used in a clinical study to determine if they will prevent late clouding of corneal grafts after the second postoperative week. In this study it has been shown that cortisone is capable of preventing the allergic response which occurs from the transplantation of tissue from one individual to another if a dose of 15 mg. per Kg. is used for 10 days.

Further, it seems that if corneal tissue can be protected from a donor-recipient sensitization for approximately six weeks, the graft will assume the individuality of the recipient. Thus, the opacification of grafts which would result from this type of allergic reaction might be averted even though the effect of cortisone lasts only while the drug is being administered.

Finally, these experiments are still further evidence that the mechanism of destruction of tissue when transplanted from one individual to another is the result of a sensitization phenomenon. They also demonstrate that this type of reaction is not one of tissue specificity, but individual specificity, because skin transplanted from the same donor caused an allergic reaction in corneal tissue.

Conclusions

1. It has been shown that an opacification of corneal grafts can be produced in rabbits by a donor-recipient sensitization.

2. The clinical appearance of the reaction

in these eyes is very similar to the clouding of mechanically successful corneal transplants in man, where the graft becomes opaque two to six weeks after operation.

3. The donor cells in a corneal graft appear to survive for about six to seven weeks after transplantation when the biologic individuality of an animal is used as a means of identifying the tissues.

4. The clouding of corneal grafts which results from a donor-recipient sensitization can be influenced by the use of cortisone.

5. The clouding of corneal grafts produced in these experiments by the supplemental transplantation of skin is further proof that the destruction of homotransplanted material is the result of a donor-recipient sensitization. It also demonstrates that an allergy so produced will affect more than one type of tissue from the same animal.

Stanford University Hospitals (15).

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STUDIES ON EXPERIMENTAL CORNEAL STORAGE*

BIBLIOGRAPHIC SURVEY: OBSERVATIONS ON WATER UPTAKE AND CORNEAL STROMA CELLS

WILHELM BUSCHKE,† M.D.
New York

(With the technical assistance of Audrey Howard, B.A., and Margaret White.)

Many methods for the preservation of corneal tissue have been recommended or tried in the past (table 1). Only a few of these methods have become popular among ophthalmic surgeons and have given clinical results comparable to those obtained with fresh donor tissue. Naturally, the clinical result will have to be the ultimate criterion for the efficiency of any procedures involved in corneal transplantation. However, in view of the large number of variables other than storage conditions which enter into the clinical result, it is important to look for and define criteria of tissue preservation which are based on observations on the stored tissue itself.

A precise definition of suitable criteria of preservation has in the past been somewhat obscured by arguments about the viability of the graft tissue as a requisite for transplantation. In particular, reported successes with formalinized grafts were considered as evidence of the futility of finding criteria for

* From the Ayer Foundation Ophthalmic Research Laboratory, Manhattan Eye, Ear, and Throat Hospital.

† It is with regret that the JOURNAL learns of the death of Dr. Wilhelm Buschke on December 21, 1950.

TABLE 1

METHODS OF CORNEAL STORAGE

Storage of the Whole Eye in	Author
Moist Chamber	Bajenova[1] Castroviejo[2] Davson[3] Duane[4] Filatov[6-7] Katzin[8] Löhlein[9] Magitot[10-11] Paufique[12] Sédan-Bauby *et al.*[13] Sourdille[14]
Cadaver at Low Temperature	Kobzar[15]
Distilled Water	Magitot[10]
Saline, Ringer or Locke Solutions	Castroviejo[2] Magitot[10-11] Welter[16]
Disinfecting Solutions	Katzin[17] Petrosiantz[18]
Serum	Castroviejo[2] Magitot[10]
Spinal Fluid or Aqueous Humor	Magitot[11] Petrosiantz[18]
Plasma	Doucet *et al.*[20]
Clotted Blood	Filatov[6] Shershevskaya[21] Welter[16]
Citrated Blood	Doucet *et al.*[20] Filatov[6-22-23] Fine[24] Jayle[25] Magitot[11] Petrosiantz[18] Sédan-Bauby *et al.*[13]
Hemolyzed Blood	Auerbach[26] Filatov[22] Magitot[10-11-13-27-28]
Hemolyzed Blood at Temperatures below 0°C.	Magitot[27]
Mineral Oil	Duane[4] Magitot[11] Sédan-Bauby *et al.*[13] Sourdille[14]
Olive Oil	Thomas[29]
Vaseline	Magitot[11]
Whole Eye Frozen	Bajenova[30]

Storage of Excised Corneas of Corneal Discs in	Author
Moist Chamber	Filatov[7]
Air without Added Fluid	Duane *et al.*[31] Filatov[7]
Saline, Ringer or Locke Solutions	Bürki[32] Cometta[33] Ničetić[34] Salzer[35]
Serum	Ničetić[34]
Hemolyzed Blood	Cometta[33] Ničetić[34]
Mineral Oil	Amsler[36] Bürki[32] Cometta[33-37]
Olive Oil	Ničetić[34] Thomas[29]
Cod-liver Oil	Bürki[32] Ničetić[34]
Vaseline	Magitot[10]
Dried State (without freezing)	Bajenova[29-40] Filatov[6-22-23]
Partially Dried State	Bajenova[29-40]
Frozen-Undried State	Bajenova[30-41] Duane[4] Filatov[7] Smelser *et al.*[42]
Frozen-Dried State	Katzin[43] Leopold *et al.*[44]
Tissue Culture	Hoffman and Messier[45-46]

Storage of Corneas After Denaturing Procedures	Author
Storage following Formalin Fixation	Deutman[47] Duane[4] Löhlein[48] Ničetić[34] Salzer[35-49-50] Shershevskaya[51] Wiener[52]
Storage of Cornea in Air, Saline, Frozen Saline, Nitrogen or Vacuum following Exposure to Fast Electrons	Duane[31]

preservation of nonfixed tissue. Research became directed more and more toward the problem of whether or not the donor tissue is eventually replaced by host tissue. Lasting successes with formalinized material seem to be rare, however, and nonfixed material is now generally accepted as superior.

It was, then, natural to search for criteria of viability as standards of preservation of nonfixed tissue. This search, however, led to some confusion in regard to the definition of a criterion of tissue preservation. A list of some criteria which have been used, together with clinical results, gross appearance, and transparency of donor tissue, is given in Table 2.

TABLE 2

CRITERIA OF PRESERVATION

Criteria	Author
Appearance of Donor Material on Examination with Corneal Microscope or Slitlamp	Castroviejo[3] Petrosiants[31] Welter[38]
Histologic Appearance of Donor Material	Castroviejo[3] Duane[21] Magitot[10] Sédan-Bauby *et al.*[12] Seidenari[53-54] Pupenko[58]
Special Histologic Features e.g. Acidophilia	Seidenari[53-54]
Loosening of Epithelium	Seidenari[53] Pupenko[58]
Cell Migration and Mitotic Activity	Filatov[7] Pupenko[58] Skorodinska[36]
Growth in Tissue Culture	Bajenova[1-40-41-47] Filatov[69-70] Kobzar[13]
Capacity to Swell	Duane *et al.*[31]
Thickness of Cornea and Water Uptake	Cometta[23] Davson[5] Papenko[58] Shesterikova[60]
Mineral Components	Davson[5] Shesterikova *et al.*[60]
Permeability to Ions	Klein[28]
Nitrogen Fractions	Shesterikova *et al.*[60]
Activity of Proteases	Shesterikova *et al.*[60]
Respiratory Activity and Activity of Specific Oxidases	Bürki[20] Duane[4-21] Filatov[7] Niketić[34] Shesterikova *et al.*[60]
Oxidation-Reduction Carriers (ascorbic acid and glutathione)	Shesterikova *et al.*[60]
Carbohydrate-Fractions	Gelefovich *et al.*[61]
Lipoid-Fractions	Shesterikova *et al.*[60-62]
Inhibitions of Bacterial Growth	Duane *et al.*[31]

Some of the criteria listed in the table were used to demonstrate viability of the tissue according to classic biologic definitions. Evidence of viability as judged by some of these criteria does not, however, necessarily imply the presence of the morphologic and functional integrity requisite for a successful take and for the maintenance of transparency.

Duane[4] was able to demonstrate, for example, that respiratory activity, as tested with the Warburg method, is quantitatively unimpaired in stored corneas for several days *beyond* the time period during which the tissue may be considered as useful for purposes of transplantation. Such a result should not occasion any surprise and is consistent with my observations,[63] that a strongly positive indophenoloxidase reaction may be found in cells of corneal epithelium isolated by various means and that, in various tissues, the functional integrity of respiratory enzymes is unimpaired even in isolated cell granules (Hermann and others).[64, 65]

Another commonly used criterion of viability, namely, the capacity of the tissue to grow in tissue culture,[1, 38–41, 57] has likewise failed to serve as a useful index for the preservation of corneal tissue for purposes of transplanation. This conclusion may be drawn from the observations of Messier and Hoffman[40] that grafts from corneas cultured in vitro fail to give satisfactory clear transplants.

More useful criteria of tissue preservation may be expected from those morphologic and physiologic properties of the tissue by which stored tissue differs from fresh nonfixed tissue under certain conditions of storage, and from factors or conditions which would diminish or abolish those differences. In addition to the expected practical usefulness for keratoplasty, such as approach should reveal some interesting physiologic information.

Some such criteria, which appear to be more intrinsically related to physiologic peculiarities of corneal tissue, are also listed in Table 2. Criteria utilizing swelling properties of the tissue,[3, 31, 33, 55, 58] for example, must be intimately connected with the physiology of corneal hydration and deturgescence. The role this plays with regard to transparency and other physiologic properties and pathologic manifestations of the cornea has been amply demonstrated.[66, 67]

The physiologic importance of hydration is further suggested by studies on the steady-state of corneal hydration[68] and of changes in hydration on storage.[58, 69] Some histologic observations on corneal stroma cells of stored corneas[13] may also be interpreted with relation to corneal hydration; this will be discussed in connection with my own histologic observations.

Favorable clinical experiences with donor material stored under exclusion of water[32, 33] indicate that the state of hydration is a most suitable criterion of preservation.

Studies on various phases of tissue metabolism (nitrogen, carbohydrates, lipoids, and others) in cold-stored corneas[4, 7, 31–33, 34, 59–62] have not thrown much light on the pathologic processes involved in tissue degeneration nor on physiologic mechanisms which would be of interest in connection with corneal preservation.

When changes were found, they were subject to very great variability. While, for example, a mean increase of 68 percent in the nonprotein-nitrogen fraction was reported for the fourth day of storage,[59] my computation of the standard deviation from the reported data gave a value as high as 43 percent of the mean. A reinvestigation of this phase seems to be indicated.

Tissue cohesion[53, 55] may also be considered as an important physiologic criterion of preservation because it can serve as an index of the integrity of tissue organization. Further observations on tissue organization may be expected to yield valuable criteria of preservation.

In the present study experimental evidence for hydration as a criterion of preservation will be substantiated and extended. Apart from the physiologic importance of the state of hydration, systematic studies of hydration, at various periods of time and under various conditions of storage, appear promising as a physiologic criterion of preservation for two additional reasons.

In the first place, physical mechanisms can be visualized by which such water uptake may occur at low temperatures, concomitant with changes in electrolyte distribution. Thus, at the conventionally used low storage temperature, water uptake may be considered as a potential early causative factor for the loss of fitness of the tissue for transplantation. This criterion would not be met by a criterion aimed, for example, at primary autolytic processes which have rather high temperature coefficients.

Fig. 1 (Buschke). Control. Fresh fixed beef cornea (Zenker). Flat paraffin section. Hematoxylin-eosin. (×470.) Normal stroma cells.

Secondly, our preliminary observations showed—in corroboration of a statement by Cogan[70]—that changes in hydration occur quite early during storage; that is, within the time period during which the tissue begins to become less fit for transplantation.

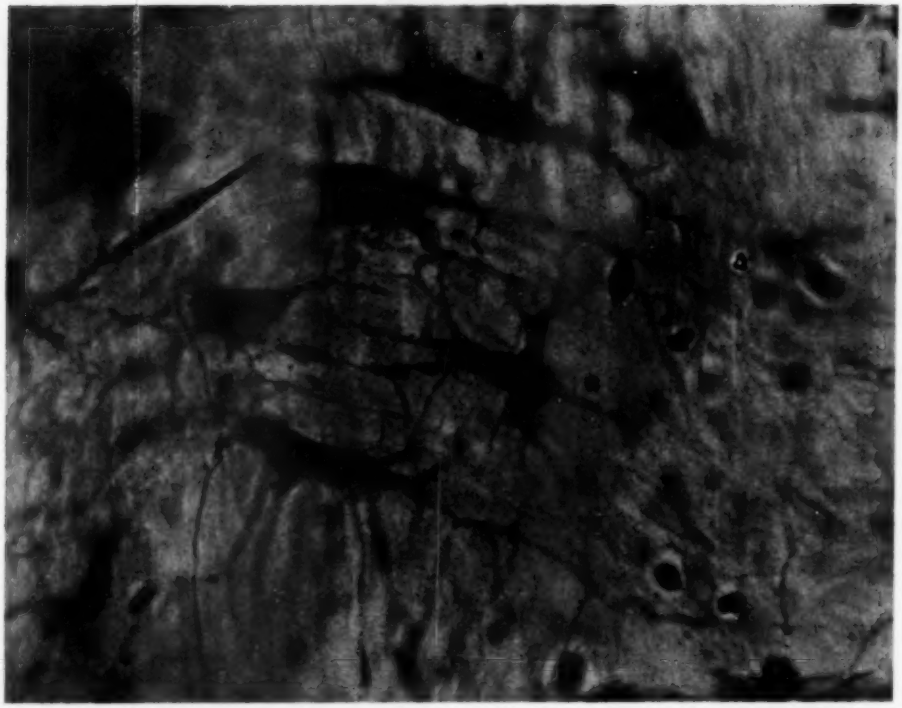

Fig. 2 (Buschke). Beef cornea. Storage of whole eye two days in moist chamber. Formalin-alcohol fixation. Flat frozen section. Hematoxylin. (×470.) Basophilic cytoplasm and communicating cell processes of stroma cells.

Materials and Methods

The experiments were performed with fresh eyes of cattle.* For the histologic observations on corneal stroma cells, both paraffin sections from Zenker-fixed or formalin-alcohol-fixed material and frozen sections from formalin-alcohol-fixed material were used. Whenever paraffin embedding was used, control material from fresh corneas was embedded in the same block with the stored experimental tissue. Both meridional and flat sections of corneas were examined.

The degree of hydration of the cornea was determined as the difference between wet weights and dry weights following dehydration of the corneas for two days at 115°C.

Storage procedures used for comparative evaluation were:

a. Storage of the whole eye in a moist chamber over cotton soaked in normal saline.

b. Storage of the whole eye in a moist chamber after replacement of the aqueous humor by mineral oil, n-hexadecane, or air.

c. Storage of the excised corneas in closed vessels of 15- or 25-ml. capacity, without any added fluid.

d. Storage of the excised cornea in mineral oil, n-hexadecane, or n-octadecane.†

e. Storage of corneas or of corneal discs of 10-mm. diameter in sealed 160-ml. vessels

* A few observations were made on corneas from human eyes kindly supplied by the Eye-Bank for Sight Restoration, Inc.

† The n-hexadecane and n-octadecane used were the commercial products of the Paragon Division, Matheson Company, Inc., East Rutherford, New Jersey.

over 80 ml. of salt solutions of various concentrations.

The storage temperature was between 2° and 7°C. throughout. Hexadecane and octadecane were used because these paraffins have melting points of 18° and 28°C., respectively, and thus are fluid at body temperature but solidify rapidly at the lower temperature of storage. Their advantage over oils is that the tissue can be freed from them even at room temperature following removal from the refrigerator at the end of the storage period.

Results

I. Histologic observations on corneal stroma cells

The corneal stroma cells, with a strikingly basophilic cytoplasm and long anastomotic cell processes, can readily be seen in the beef cornea, particularly in flat sections and after some degree of swelling of the corneal stroma has occurred. Vollaro made use of this latter phenomenon by "macerating" pieces of cornea in 20- to 30-percent potassium hydroxide for several hours prior to embedding or sectioning.

Fig. 3 (Buschke). Beef cornea. Whole eye stored three days in moist chamber (Zenker). Flat paraffin section. Hematoxylin-eosin. (×470.) Swollen stroma cells.

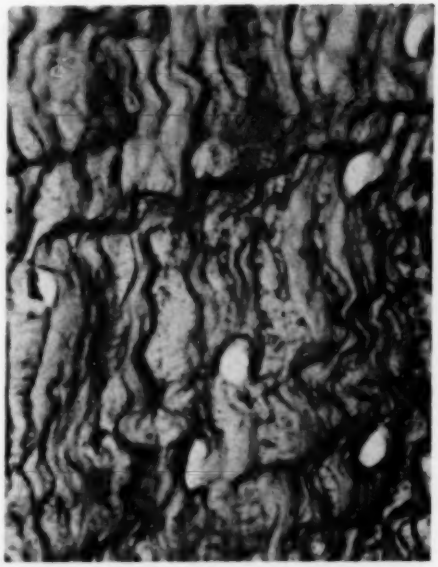

Fig. 4 (Buschke). Beef cornea. Whole eye stored five days in moist chamber (Zenker). Ordinary paraffin section. Hematoxylin-eosin. (×470.) Stroma cells swelling.

While I do not wish to enter here into the somewhat controversial discussion about the presence or absence of elastic fibers in the cornea and their possible relation to cell processes of the stroma corpuscles, I can confirm that the cell processes can be very plainly seen after procedures producing corneal swelling. Among these procedures, storage of the whole eye in a moist chamber in the cold seems to be the simplest one (fig. 2).

In addition I have observed a quite characteristic change of the stroma cells—a balloonlike swelling by which the nucleus of the cell is flattened and apparently pushed

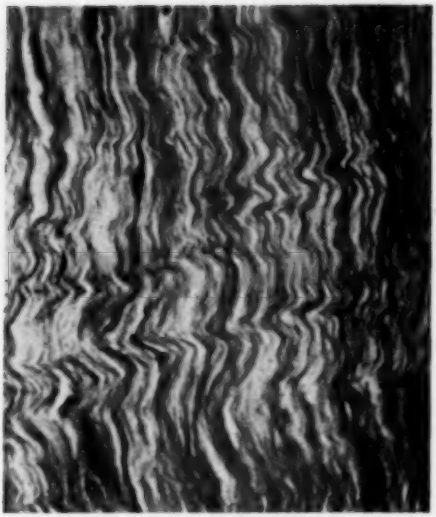

Fig. 5 (Buschke). Control fresh beef cornea (Zenker). Ordinary paraffin section. Hematoxylin-eosin. (×470.) No stroma cell swelling.

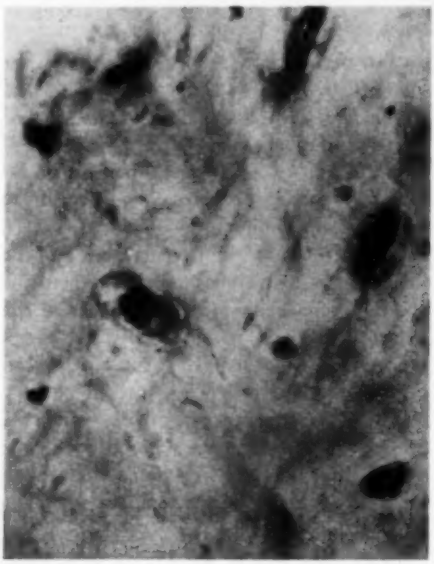

Fig. 6 (Buschke). Beef cornea. Whole eye stored 10 days in moist chamber. Formalin-alcohol fixation. Hematoxylin. (×470.) Vacuoles in cytoplasm of stroma cells.

toward one side. This may be seen both on ordinary vertical and on flat sections and is somewhat more conspicuous in sections from paraffin embedded material (figs. 3, 4, and 9).

In the earlier stages, vacuoles are found in the cytoplasma which then assumes a reticu-

Fig. 7 (Buschke). Human cornea. Whole eye stored five days in moist chamber. Formalin-alcohol fixation. Hematoxylin. (×470.) Reticulated and swollen cell bodies.

lar structure in contrast to its more homogenous appearance in sections from fresh tissue (figs. 6 and 7).

The more positive balloonlike appearance seen in paraffin sections should not detract from the fact that the phenomenon was also observed in frozen sections and that it was conspicuously absent in the control sections of fresh paraffin-embedded corneas which

were carried along in the same block and dehydrated and stained on the same slide (figs. 1, 5, and 8). As may be seen in Figure 3, the phenomenon was well developed after three days of storage of the whole eye in a moist chamber, and it affected a progressively larger number of cells on continued storage thereafter.

The large balloonlike space did not stain with the ordinary histologic stains. The phenomenon was absent or much less marked in corneas which had been stored in mineral oil (fig. 8), but it could be found in corneas stored in air which did not show any net water uptake on weighing.

II. Quantitative data on hydration

Data on fluid uptake of the cornea under various storage conditions are summarized in Table 3.

It is particularly noteworthy that with the most widely used storage condition—storage of the whole eye in a moist chamber—a significant water uptake is found as early as eight hours following removal of the eyes from the killed animal (between six and eight hours of cold storage). A significant water uptake has already taken place even though inspection of the cornea at this time does not indicate even slightly that it is not an absolutely fresh cornea. Within the next few days, this water uptake reaches considerable proportions.

For the first few days at least the fluid uptake appears to follow a quite regular, constant course, under my experimental conditions, as may be seen from the low values of the standard deviations of the percent water contents. Our data are in agreement with the data for fresh corneas reported by others,[55, 68, 69] with a qualitative statement by Cogan[70] on fluid uptake in the first few hours

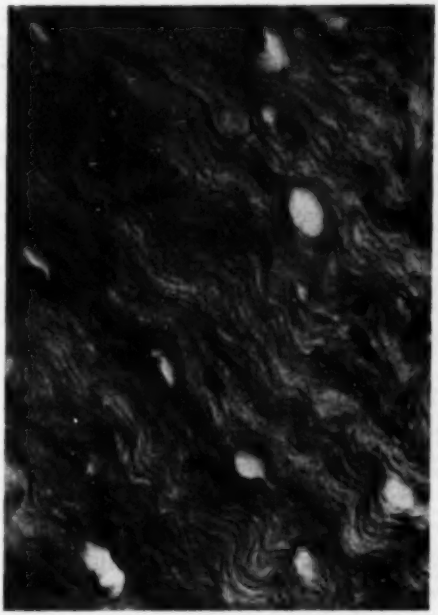

Fig. 9 (Buschke). Beef cornea. Stored, after excision, in air in closed vessel for four days. Flat paraffin section. Hematoxylin. Some swollen stroma cells.

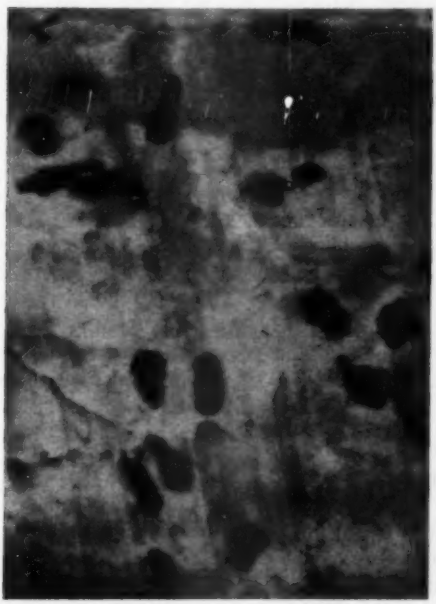

Fig. 8 (Buschke). Human corneal discs, stored in mineral oil for 12 days at 8°C. Formalin-alcohol fixation. Flat paraffin section. Hematoxylin-eosin. (×470.) Cell bodies and cell processes barely visible, not hydropic.

TABLE 3

WATER CONTENT OF BEEF CORNEAS ON STORAGE

(in percent)

Duration of Storage	0 (fresh)	8 hours	1 day	2 days	3 days	4 days	6 days	8 days	10 days	12 days	14 days
Storage Procedures											
Whole eye in moist chamber (aqueous not removed)	32 74.5–83.8 *78.4* (1.9)	12 80.2–83.2 *81.6* (0.8)	12 81.6–82.9 *82.3* (0.4)	17 83.6–85.6 *84.6* (0.6)	7 85.1–86.1 *85.5* (0.4)	2 85.8–86.2 *86.0*	3 88.6–89.1 *88.8*	3 89.4–90.0 *89.7*	2 89.8–90.5 *90.2*		
Whole eye in moist chamber (aqueous replaced by mineral oil)				3 78.9–81.2 *80.4*							
Whole eye in moist chamber (aqueous replaced by n-hexadecane)			14 77.1–81.4 *79.1* (1.4)	12 75.6–88.4 *80.4* (3.5)	23 79.7–88.1 *84.3* (2.6)	16 79.1–84.1 *81.6* (1.3)	13 73.7–86.1 *81.3* (2.8)	3 78.5–85.4 *81.2*	3 81.1–86.1 *82.2*	3 81.1–86.1 *82.9*	2 81.0–82.9 *81.9*
Whole eye in moist chamber (aqueous replaced by air)				3 78.1–79.3 *78.7*		3 80.8–83.9 *82.7*	3 80.1–83.1 *81.5*			3 83.7–84.3 *84.0*	
Whole eye in moist chamber (epithelium removed and aqueous replaced by hexadecane)				80.9–86.9 *83.9*		81.9–89.3 *86.1*	81.9–84.1 *83.3*				
Whole eye (with cornea immersed in mineral oil)				2 84.0 *84.0*							
Whole eye (with cornea immersed in hexadecane)				3 84.6–85.1 *84.9*		3 86.3–86.8 *86.6*	3 87.6–88.1 *87.9*				
Whole eye (up to limbus in hexadecane, aqueous in front of cornea)				3 82.7–88.4 *86.3*		3 83.5–88.2 *85.5*					
Excised cornea (in air in sealed vessel of 25-ml. cap.)										7 73.5–77.8 *76.7* (1.5)	
Excised cornea (with scleral lip, suspended over M/7 NaCl)					9 79.5–82.1 *80.8* (0.8)						
10-mm. Discs (over M/7 NaCl)							10 78.7–85.3 *83.5* (1.9)				
10-mm. Discs (over M/3 NaCl)							9 71.9–84.5 *79.2* (4.8)				
10-mm. Discs (over M/2 NaCl)							15 75.0–83.1 *78.9* (3.1)				
10-mm. Discs (over 0.75 M)							10 71.5–76.4 *74.2* (1.5)				

Legend of figures in each box:

No. of Samples
Minimum-Maximum
Mean (S.D.)

following enucleation, and with the data given by Shesterikova and Rapoport[38] on percentage of solid content during two weeks of storage.

In contrast, less fluid uptake is found in the corneas of eyes stored in a moist chamber following replacement of the aqueous by air, mineral oil, or hexadecane. The large scattering of these data, however, raised some interesting questions to be discussed later in this paper.

If the eyeball or the anterior portion is submerged in oil or hexadecane, fluid is taken up by the cornea to at least the same degree as in ordinary storage in a moist chamber. Isolated corneas suspended on a scleral lip in a moist chamber over salt solutions take up much less fluid during several

days of storage. The fluid uptake of corneal discs of 10-mm. diameter (beef), stored over various concentrations of watery solutions of sodium chloride, is at a minimum over about 0.5 molar NaCl.

In addition to these studies on hydration during storage under various conditions, observations have been made on nitrogen fractions, that is, nonprotein nitrogen, ammonia-N, and aminoacid-N, as well as on cell cohesion in the epithelium and endothelium of stored corneas.

These studies were made in order to establish whether differences could be found between fresh and stored tissue if the tissue was incubated for several hours subsequently to cold storage. Under these conditions, the circumstances of surgically transplanted tissue are realized to some degree.

The results showed increases in the nonprotein nitrogen fraction and ammonia-N fractions in those corneas which had been stored in the whole eye with subsequent incubation for several hours at higher temperature, as compared with fresh incubated corneas.[72]

Discussion

It is obvious that the progressive hydration of the cornea during cold storage of the whole eye in a moist chamber is due predominantly to the uptake of fluid from the interior of the eye itself.

In addition to fluid uptake from the aqueous, one also has to consider in these experiments the limbal region as a potential portal of entry for fluid diffusing through the sclera from other portions of the eye. This possibility has to be considered particularly because quite high hydration values were found in some of our experiments when the aqueous humor had been replaced by other, nonaqueous media. The uncontrolled factor or factors responsible for this large scatter in the experiments with replacement of aqueous by nonaqueous media are still to be determined.

However, the experimental results obtained with corneas which were suspended over various concentrations of NaCl in solution indicate that, even in the absence of the aqueous, at the temperature conventionally used for cold storage, a vapor pressure over a NaCl solution of a concentration of less than 0.5 M. is not in equilibrium with the forces determining hydration or deturgescence of the cornea at this temperature.

It should be mentioned here that, in the presence of the lining epithelial cellular membranes of the suspended cornea, deviations from the conditions of equilibrium as, for example, dehydration on suspension over more concentrated solutions, may manifest themselves only after considerable periods of time. In order to determine the equilibrium condition, it was therefore necessary to do these experiments either on denuded corneas or on smaller (10-mm. diameter) discs of beef cornea.

An essential role in the abstraction of water from the cornea in vivo has been attributed to osmotic forces operating across the intact epithelium and endothelium and with the help of hypertonic tears and aqueous humor.[71]

Davson[69] has challenged this notion on the basis of his own data and considerations on the concentrations of osmotically active ions in the cornea, and of those in the literature on ionic concentrations in the aqueous humor and in the tears.

The histologic observations on the corneal stroma cells reported here suggest the possibility that these cells may have a physiologic function in corneal deturgescence. The marked vacuolar and hydropic swelling of the corneal stroma cells which is most striking in corneas from eyes stored in a moist chamber suggests that these cells take up fluid under the conditions of storage.

Similar histologic observations have been made and described as "halo clair perinucleaire" by Sedan-Bauby *et al.*[12] on corneas of stored dogs' eyes, although these authors

interpreted the changes as signs of degeneration or necrosis of the stroma cells.

In connection with these observations, it is tempting to speculate about the possibility that the corneal stroma cells have some essential function in fluid elimination which may be impaired or interfered with under the unphysiologic conditions of cold storage.

Davson[71] has previously suggested the possibility "that the corneal corpuscles are capable of activity that reduces the collagen's power to turgesce." These considerations should, however, not distract from a consideration of the roles of the endothelium and epithelium in possible additional mechanisms of deturgescence.

Summary

1. A bibliographic survey has been presented on methods of preservation of corneas and of criteria not based on the clinical success of transplant operations. Various criteria have been compared with respect to their pathophysiologic importance.

2. The water uptake of beef corneas has been followed under various conditions of storage from the first hours through several days of storage. In the whole eye, the cold stored cornea shows a significant increase of water content as early as eight hours after death of the animal.

3. A most conspicuous alteration of the corneal tissue is the "hydropic" swelling of the stroma cells. In earlier stages of corneal swelling, basophilic cytoplasm of corneal stroma cells and anastomotic cell processes are readily seen.

4. The histologic changes in the corneal stroma cells have been discussed with respect to the possible role of the stroma cells in corneal deturgescence.

210 East 64th Street (21).

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Dr. Olga Sitchevska made available some of the original Russian literature.

Dr. Albrecht Buschke translated and abstracted some of the Russian literature.

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AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN IN EXPERIMENTAL HERPES-SIMPLEX VIRUS INFECTIONS*

HILDEGARD ODENHEIMER GELLER, M.A., AND PHILLIPS THYGESON, M.D.
San Jose, California

Before the introduction of aureomycin, no serious claims had been made that any of the sulfonamides or antibiotics were effective in the treatment of experimental or clinical infections with any of the typical viruses. Aureomycin was soon recognized to be effective against the rickettsiae and the atypical viruses of the psittacosis, lymphogranuloma venereum, trachoma group, and the work of Braley and Sanders[1] suggested that the spectrum of activity of this remarkable antibiotic might also be broad enough to include herpes-simplex virus and the virus of epidemic keratoconjunctivitis. Subsequent clinical studies[2] indicated that the virus of herpes zoster might also be susceptible.

The claims of Braley and Sanders with respect to clinical results in dendritic keratitis received some support from Appelman and Hale,[3] in 1949, and from Thygeson and Hogan,[4] who reported the favorable effect of topical aureomycin borate in about 60 percent of a small series of cases. Allen[5] reported a number of favorable results but concluded that there were some totally resistant strains of the virus.

Successful results were also obtained by Zeller[6] and there have been a number of reports[7] of the effective treatment of oral infections. Duke-Elder, Ainslee, and Boase,[8] on the other hand, found the antibiotic totally ineffective in a small series of herpetic keratitis cases.

Braley and Alexander[9] conducted a series of laboratory studies which indicated that aureomycin inactivated herpes-simplex virus in in vitro experiments, that it increased the survival time of mice infected intracerebrally, and that it was effective in experimental rabbit keratitis if used early in the disease. Baldridge and Blank,[10] on the other hand, found the antibotic to have no in vitro action on the virus, and no significant in vivo action, in a series of chick-embryo experiments.

At the time of writing, no reports of experiments concerned with the effect of chloromycetin or terramycin on herpes virus are to be found in the literature, but in a personal communication from Quilligan[11] it was reported that terramycin had increased slightly the survival time of intracerebrally inoculated mice but had not prevented a fatal outcome.

The following rabbit and mouse studies were undertaken in an effort to obtain further information on this controversial subject. The virus strain which was used in all but one experiment was procured on October 26, 1948, from a patient with typical dendritic keratitis. It is noteworthy and possibly significant that the clinical disease in this patient resisted topical applications of aureomycin borate but responded to cauterization with tincture of iodine. In one experiment a virus strain was used which had been isolated by Dr. E. Jawetz from a herpetic skin lesion.

AUREOMYCIN STUDIES*

ANIMALS AND MATERIALS

The rabbits used in these studies were albinos. Swiss mice with an average weight of 20 gm. were used in Experiments 2 through 8; ABC mice of the same weight were used in Experiment 1.

* From the Division of Ophthalmology and the Francis I. Proctor Foundation for Research in Ophthalmology of the University of California School of Medicine. Aided by a grant from the Gustavus and Louise Pfeiffer Research Foundation.

* Aureomycin was supplied by the Lederle Laboratories Division of the American Cyanamid Company, New York.

The aureomycin hydrochloride from capsules was dissolved in acacia solution and administered orally under light ether anesthesia. The local aureomycin borate was diluted with distilled water. The parenteral preparation was dissolved in the special diluent for intravenous aureomycin which contains 0.742-percent sodium carbonate.

METHODS OF STUDY AND RESULTS IN ALBINO RABBITS

1. *Local therapy.* In Rabbit-Experiment 1, the rabbit developed keratoconjunctivitis in both eyes two days after inoculation with herpes-simplex virus by the corneal scarification method. On the following day two drops of topical aureomycin borate were instilled in one eye every 30 minutes for a total of 13 times. No treatment was given during the night. There was no significant difference in the clinical course of the disease in the two eyes and both developed leukomas. The animal exhibited symptoms of cerebral involvement and was killed 10 days after treatment had been discontinued.

In Rabbit-Experiment 2, treatment with topical aureomycin borate was begun in one eye of a rabbit at the end of the second day after virus inoculation of the cornea; treatment was continued the next day for eight hours, and again on the following day for two hours; the drops were instilled at half-hour intervals throughout all treatment periods. At the time treatment was started, one eye showed no sign of infection, the other eye very slight signs. This was the eye subjected to treatment. On the third treatment day the infection was full blown in both eyes and in eight more days the animal was dead.

2. *Intramuscular therapy.* In Rabbit-Experiment 3, a 2,200-gm. rabbit developed keratoconjunctivitis two days after corneal scarification and inoculation with the virus. The next day the rabbit was given two intramuscular injections of 0.85 mg. each, the dose calculated for the rabbit on the basis of the Lederle Laboratories recommendation for a 150-lb. man. After a pause of two days, this dose was tripled and given daily for seven days. Eight days after treatment had been discontinued, the rabbit showed a characteristic leukoma and pannus.

In Rabbit-Experiment 4, the same amount of drug was used, also intramusculârly, but the lower dose was given on two successive days before inoculation with the virus, and again on the day after inoculation, and then the tripled dose for five more days. The eyes remained relatively clear but severe cerebral symptoms developed and the animal had to be killed.

3. *Intravenous therapy.* In Rabbit-Experiment 5, intravenous treatment with aureomycin was begun three days after corneal inoculation with the virus. A dose of from 10 to 12.5 mg., given twice a day for two days, did not prevent the formation of exudate. Treatment was continued for two more days when a pannus began to form in both eyes. Forty days later one eye showed a small central opacity. The other eye, which was clear, was reinoculated with herpetic exudate but no new infection resulted.

A control rabbit inoculated with herpetic exudate from the same source developed a typical infection. It may be deduced from this experiment that the initial infection was typical but was probably modified by the use of intravenous aureomycin.

In Rabbit-Experiment 6, 50 mg. of parenteral aureomycin were given intravenously one day after corneal inoculation with the virus. On the same day drops were applied topically every half hour for eight hours. This regime was repeated the next day, but on the following day only the local treatment was continued. The total amount of aureomycin given was 150 mg. intravenously and 75 mg. locally. The animal did not develop a clinical ocular disease.

A control rabbit inoculated with material from the same source developed a mild infection and was in turn able to infect other rabbits. As a matter of fact, this animal was

used to reinfect the right eye of the original test rabbit. Three days later there was slight injection in the reinoculated eye. On the following day the eye had almost cleared and nine days later the animal died with signs of encephalitis but with apparently normal eyes. Unfortunately the significance of this experiment cannot be evaluated as treatment was not continued during reinfection.

4. *Subconjunctival therapy.* In Rabbit-Experiment 7, the rabbit was given 2.0 mg. of parenteral aureomycin twice a day by injection into the palpebral conjunctiva. This treatment was instituted on the second day after the inoculation of one eye with the virus, coincidentally with the first signs of herpetic keratitis. The next day there was a large amount of exudate. Treatment was continued for two days. Nine days later the control animal died. Forty-three days after the inoculation of the one eye as described above, the other eye was inoculated in the same manner. It developed a mild infection which terminated in a small scar. The treated eye was opaque and still slightly hyperemic 10 months later.

In Rabbit-Experiment 8, 1.0 mg. of aureomycin was injected into the bulbar conjunctiva twice before inoculation with the virus, then once after inoculation. After a pause of one day, injections of 1.0 mg. daily were resumed for two more days. The infection pursued its usual course and the rabbit was moribund, with maximum involvement of the eyes, after seven more days.

In Rabbit-Experiment 9, the same procedure was followed except that the aureomycin was given on successive days without a one-day pause. The infection followed approximately the same course.

Summary. In nine rabbit experiments in which aureomycin was administered to rabbits inoculated with herpes-simplex virus by various routes, the experimental disease in seven was not modified. In two rabbits treated intravenously the disease appeared to be modified in one and prevented in the other.

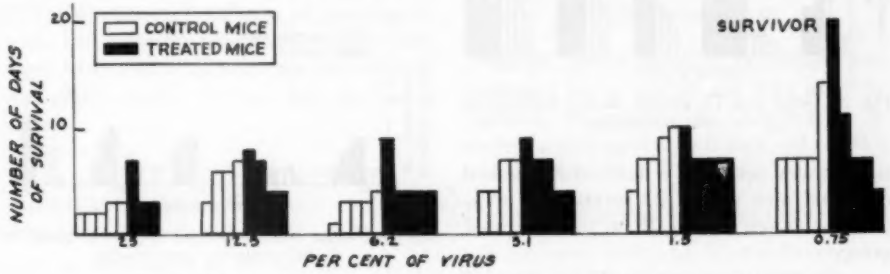

Fig. 1 (Geller and Thygeson). Mouse-Experiment 1. *In vitro* aureomycin.

Methods of study and results in mice

A number of different dilutions of the virus suspension were employed in each mouse experiment. As is clearly indicated in Figures 1 through 10, four or five tenfold dilutions of an initial 25-percent or 50-percent dilution were run in most of the test series. In Experiments 1 and 9, the initial 25-percent dilution was diluted 50 percent for each of the four or five subsequent dilutions.

In the majority of the mouse experiments approximately 25 test mice and 25 control mice were used.

1. *In vitro tests.* In Mouse-Experiment 1, in which ABC mice were used, 1.0 mg. of parenteral aureomycin per cc. of virus suspension was incubated at room temperature for one-half hour; each mouse received

0.03 cc. of the mixture, that is, 0.03 mg. of aureomycin, intracerebrally. The difference in the results between this test group and its control group was negligible (fig. 1).

In Mouse-Experiment 2, performed four months later with Swiss mice, 4.0 mg. of aureomycin per cc. of virus suspension were incubated at room temperature for one hour. As may be seen in Figure 2, there was a

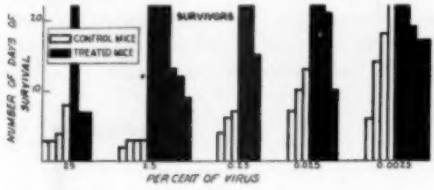

Fig. 2 (Geller and Thygeson). Mouse-Experiment 2. *In vitro* aureomycin.

considerable delay in the death of the treated mice and nine out of 20 survived as compared with one out of 18 in the untreated group.

2. *Prophylactic tests.* In Mouse-Experiment 3, the test mice were given daily 1.0 mg. of parenteral aureomycin subcutaneously

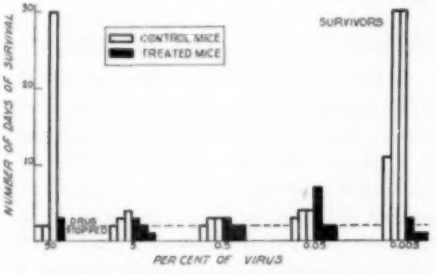

Fig. 3 (Geller and Thygeson). Mouse-Experiment 4. Subcutaneous aureomycin.

for two days. The second injection was followed in five hours by intracerebral inoculation with a 50-percent virus suspension to one group and with five successive tenfold dilutions to other groups. One mg. of aureomycin was given subcutaneously to all groups for the next three days and, after a pause of two days, for another five days. There was an insignificant delay in death among the mice receiving the more concentrated virus suspensions, and an increase in the percentage of survivors among the mice receiving the more dilute virus suspensions.

In Mouse-Experiment 4, the prophylactic dose was 5.0 mg. of aureomycin, administered subcutaneously for two days. The second injection was followed in five hours by inoculation with the virus. Shortly after the first injection of aureomycin the mice showed toxic symptoms and all died sooner

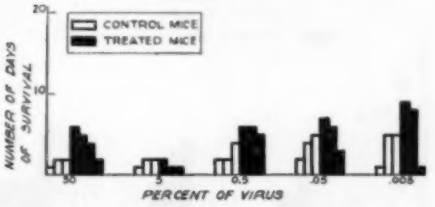

Fig. 4 (Geller and Thygeson). Mouse-Experiment 5. Subcutaneous aureomycin.

than usual, probably as a result of the toxic effect of the large amounts of the drug (fig. 3).

In Mouse-Experiment 5, daily subcutaneous injections of 2.5 mg. of aureomycin were given for two days, the second injection being followed after a few hours by virus inoculation. The next day 2.5 mg. were given, then 1.0 mg. on each of the three following days, a pause of one day, and then

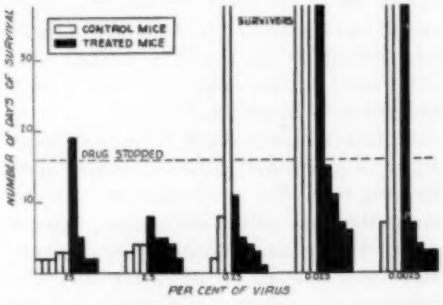

Fig. 5 (Geller and Thygeson). Mouse-Experiment 7. Oral aureomycin.

1.0 mg. per day for three more days. As may be seen in Figure 4, there were no survivors but there was a slight delay in the time of death of the treated mice.

In Mouse-Experiments 6 and 7 (fig. 5), three daily administrations of 25 mg. a day of oral aureomycin were given prior to inoculation with the virus and continued for 16 days after inoculation, or until all test mice were dead. The results were essentially negative.

3. *Treatment after inoculation.* In Mouse-Experiment 8, treatment was started immediately after inoculation with the virus. Daily injections of 1.0 mg. of aureomycin were administered subcutaneously for five days. After a two-day pause the last survivor was given another 1.0 mg. but died soon after.

Chloromycetin studies

Animals and Materials

Only a single albino rabbit was used in these studies, owing to the lack of a soluble

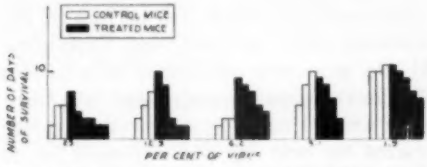

Fig. 6 (Geller and Thygeson). Mouse-Experiment 9. *In vitro* chloromycetin.

parenteral chloromycetin preparation. Swiss mice with an average weight of 20 gm. were used in experiments 9, 10, 13, 14, and 15, and mice of the ABC strain in Experiments 11 and 12. The oral preparation was dissolved in acacia and administered under light ether anesthesia. The solubility of the parenteral crystalline chloromycetin in water was 0.25 percent.

Method of study and result in an albino rabbit

In Rabbit-Experiment 10, the animal was given 0.1 cc. of the chloromycetin solution subconjunctivally once a day for three days, the third injection being followed by corneal inoculation with herpes-simplex virus. Two days later keratoconjunctivitis had developed.

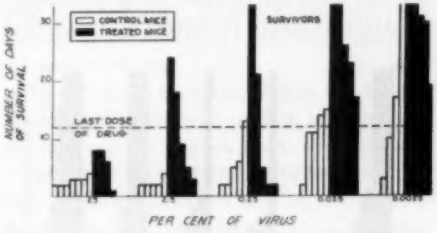

Fig. 7 (Geller and Thygeson). Mouse-Experiment 11. Oral chloromycetin.

Although subconjunctival injections were continued for a total of six days after inoculation, the animal died 12 days after inoculation with an opaque cornea and cerebral involvement.

Methods of study and results in mice

1. *In vitro tests.* In Mouse-Experiment 9, crystalline chloromycetin, with a maximum solubility of 0.25 gm. in water, was incubated with the virus suspension in a series of dilutions at room temperature for one hour before intracerebral inoculation into mice. There was a slight increase in survival time among the mice receiving the high concentrations of virus but none among those receiving the lower concentrations (fig. 6).

In Mouse-Experiment 10, the same drug was used in two groups of test mice; in one group the virus dilutions were varied and a constant amount of chloromycetin (6.0 μg.) was added; in the other group various amounts of chloromycetin were added to a constant amount of five-percent virus. There was no appreciable difference in results between the two test groups or between them and the control group.

2. *Prophylactic tests.* Mouse-Experiment 11 showed very promising results, as may be seen in Figure 7. For two days 10 mg. of oral chloromycetin were fed to a group

of mice, and the second feeding was followed by intracerebral inoculation with the virus. The daily dose of 10 mg. of chloromycetin was continued for 12 more days. There was not only a marked increase in the percentage of survivors and in the length of time before death occurred as compared to the controls, but the mice survived longer in the late stage of the disease than had any previous group of test mice.

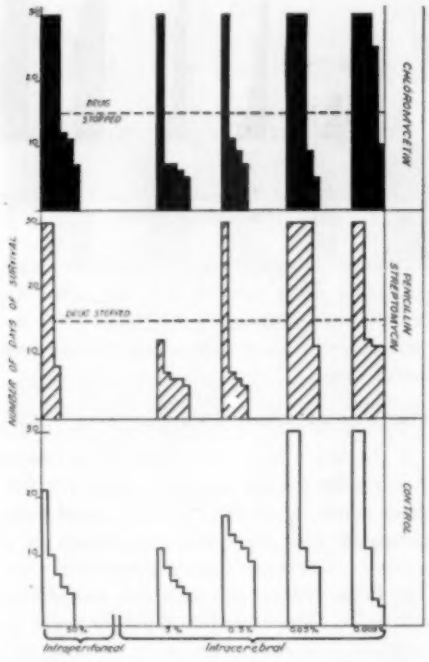

Fig. 8 (Geller and Thygeson). Mouse-Experiment 13. Oral chloromycetin.

At this time the suggestion was made to us that the promising results in this and another chloromycetin experiment were due, not to the action of the drug on the virus, but to its action on the bacterial flora of the mice which otherwise became invasive as a result of the virus action.

Two experiments with streptomycin and penicillin were devised to test this point. In addition to the usual groups of test mice and control mice, a third group was added which was treated with 2,000 units of penicillin intramuscularly, and with 5.0 mg. of streptomycin intraperitoneally, every time the other test group was fed its dose of chloromycetin.

In Mouse-Experiment 12, 4.0 mg. of chloromycetin per day were given orally on two successive days before inoculation with virus, and on 13 successive days thereafter. The results in the three groups of mice were almost identical.

Mouse-Experiment 13 varied from the above in two respects; the dose of oral chloromycetin was 10 mg. per day, and treatment was continued for 15 days after virus inoculation. Careful study of Figure 8 reveals that the penicillin-streptomycin group had a slight edge over the control group with respect to survivors and delay in death, and that the chloromycetin group in turn did slightly better than the penicillin-streptomycin group. The differences were too small to warrant any conclusions.

3. *Treatment after inoculation.* In Mouse-Experiment 14, which was performed immediately after the promising Experiment 11, the mice were inoculated with various dilutions of virus suspension, and daily treatment with 10 mg. of oral chloromycetin was started the next day and continued for 31

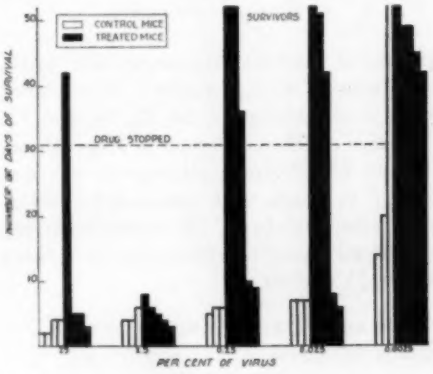

Fig. 9 (Geller and Thygeson). Mouse-Experiment 14. Oral chloromycetin.

days. In addition, subcutaneous or intraperitoneal injections of 0.2 cc. of the parenteral crystalline chloromycetin were given once daily for a few days.

The results, as presented in Figure 9, were very encouraging. Four test mice, but only one control mouse, survived, and the rest of the test group lived much longer than the rest of the untreated group. It was noted too, during the course of the experiment, that one mouse that had received 25-percent virus and one that had received 0.25-percent virus seemed to recover from very severe infections after two weeks, but finally died on the 11th and fifth days, respectively, after treatment was stopped.

In Mouse-Experiment 15, performed six and one-half months later, the streptomycin-penicillin group was included as an additional control; 4.0 mg. of oral chloromycetin daily were administered after inoculation with the virus and this dose was continued for a total of 18 days. The results were equivocal, the chloromycetin-treated group showing an advantage in one instance, the penicillin-streptomycin-treated group in another, and the controls in still others.

Terramycin studies

Animals and Materials

In the small series of experiments with this drug completed at the time of writing, only four albino rabbits and two groups of Swiss mice had been used. The oral terramycin hydrochloride was dissolved in acacia and administered under light ether anesthesia, and the topical terramycin borate was dissolved in distilled water.

Methods of study and results in albino rabbits

1. *Terramycin drops.* In Rabbit-Experiment 11, an albino rabbit was inoculated bilaterally with herpes-simplex virus. Two days later typical herpetic figures and exudate had developed. Two drops of terramycin were instilled in one eye every hour for eight hours on three successive days, for three hours only on the two following days, then again for eight and six hours, respectively, on the next two days. By this time the treated eye, which until then had seemed less involved than the untreated eye, also showed active infiltration although less than the untreated eye.

Twelve days after inoculation the treated eye showed slight conjunctival activity with minimal corneal opacification, while the untreated eye showed dense corneal opacity with pannus formation and an active conjunctivitis. One day later the animal was dead.

Rabbit-Experiment 12 was a repetition of Experiment 11 except that a separate animal was used for the control eye. Two rabbits were inoculated with herpetic material in the usual manner. Three days later one rabbit showed a mild conjunctivitis with very little exudate, and a keratitis. Topical terramycin was administered hourly for eight hours and continued on an eight-times-per-day basis for a total of five days. During the next two days only three applications were given but for the succeeding five days the eight-times-per-day schedule was resumed.

There was a noticeable difference between the treated and the control eyes in favor of the former although both rabbits developed only a very mild type of infection with minimal conjunctival reaction. Eighteen days after inoculation the conjunctival injection in both eyes had subsided. Each eye showed a corneal opacity but the one in the treated eye was only half as large as the one in the untreated eye. This difference was not considered great enough to warrant any definite conclusions.

In connection with this experiment, it must be noted that by this time the virus had changed and was producing a clinical picture more closely resembling the human type of herpetic ocular infection, with a severe keratitis, a very mild conjunctivitis, and complete, or almost complete, absence of exudation.

2. *Terramycin ointment.* In Rabbit-Experiment 13, one rabbit was inoculated bilaterally with washings from the infected eye of the animal used in Experiment 12. Three days later there was evidence of a mild conjunctivitis with very little exudation. After another two days, treatment in one eye was begun with terramycin ointment, hourly for eight hours, and continued for three days. There was no noticeable difference between the treated and the untreated eyes except for a more pronounced hyperemia in the treated eye. The rabbit was dead on the fourth day after treatment had been discontinued.

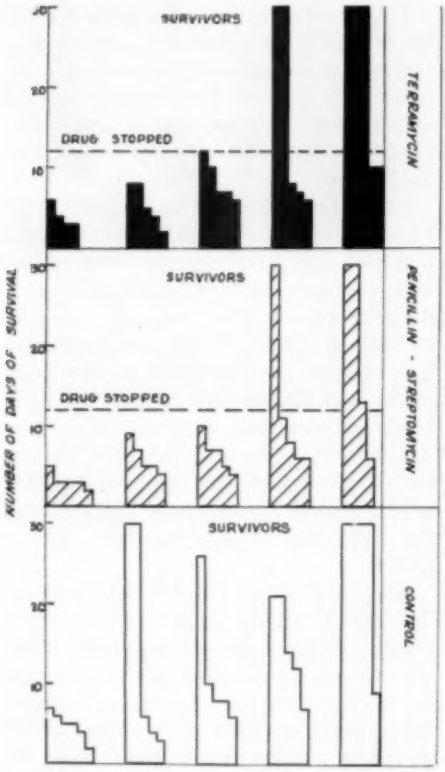

Fig. 10 (Geller and Thygeson). Mouse-Experiment 16. Oral terramycin.

Methods of study and results in mice

In Mouse-Experiment 16, one group of mice was given 10 mg. of terramycin orally three days prior to inoculation with virus and another group was given intramuscular penicillin and intraperitoneal streptomycin instead. Treatment was continued for 16 days after inoculation with virus. As may be seen in Figure 10, no advantage accrued from the use of the terramycin.

Mouse-Experiment 17 was a repetition of Experiment 16 but with a larger number of mice and a new virus. This virus, designated as the Maxwell virus by Dr. E. Jawetz of the Department of Bacteriology, University of California, was isolated March 5, 1950, from a recurrent herpetic skin lesion from the arm of a patient. It had produced keratitis in one rabbit and encephalitis in another, and had been propagated through three chorioallantoic-membrane passages and three mouse-brain passages. Immediately after intracerebral inoculation of the mice with virus, a daily dosage of 10 mg. of oral terramycin was instituted and continued for eight days. There was no difference between the results in the control mice, the penicillin-streptomycin-treated group, and the group treated with terramycin.

Discussion

The possibility suggested by Allen that strain differences may be significant is difficult to evaluate as yet. In interpreting the results reported here, however, it should be borne in mind that the strain used was from an aureomycin-resistant dendritic keratitis; that, although only one strain was used, the early experiments could not be repeated with the same satisfactory results; and that the steady increase in the percentage of deaths from encephalitis among rabbits inoculated in the cornea would indicate that the strain had become more neurotropic during the course of the experiments.

Multiplicity of immunologic strains has

been recognized for herpes-simplex virus by Slavin and Gayett[12] and by Florman and Trader,[13] and dermatotropic and neurotropic strain differences are known to exist.

It is unfortunate that experimental herpetic keratitis in the rabbit differs from its human counterpart in being more severe and less amenable to therapy. Chemical cauterization with iodine and other agents, which has a high incidence of success in human cases, has been valueless in the experimental infection.

This is probably because in the rabbit the virus passes rapidly into the corneal nerves, a fact which may be deduced from the frequency of sequential encephalitis. This makes the poor results obtained from the local use of the three antibiotics less conclusive than they otherwise would be.

An attempt is now being made to develop by preliminary immunization a clinically comparable infection in the rabbit such as was obtained by Woods in experimental tuberculosis with the so-called "immune-allergic rabbit."

In a personal communication, Braley[14] has stated his belief that early samples of aureomycin were much more active in dendritic keratitis than the later, more purified preparations of the antibotic, and has even suggested that the antiherpetic factor might be an impurity. This is a possibility that requires investigation in view of the decreasing clinical success with aureomycin borate in human infections which has been noted by a number of observers.

It has been suggested[15] that the antibiotics may have a nonspecific action by which they may prevent or delay terminal bacterial invasion from the intestinal or respiratory tracts, and that this could be responsible for the increased survival times in mice which have been noted by Braley and Alexander, and to a lesser extent by us, particularly in connection with the use of oral chloromycetin. Preliminary experiments designed to compare the effect of streptomycin and penicillin which are known to have no antiherpetic action, with the effect of the three antibiotics under discussion, have so far proved inconclusive.

We are aware of the fact that the number of test animals involved in this study is too small for satisfactory statistical presentation of the results, and that an additional number of mice and rabbits will have to be tested. However, the results obtained in this series of experiments would seem to indicate a trend worthy of further investigation.

Summary and Conclusions

1. Experiments were conducted to test the effect of the antibiotics aureomycin, chloromycetin, and terramycin on experimental herpes-simplex virus infection of the rabbit cornea and the mouse brain.

2. It was impossible to prevent or modify experimental herpes keratitis in the rabbit with topical, intramuscular, or subconjunctival administration of aureomycin. The course of the disease appeared to be modified, however, by intravenous administration of from 40 to 50 mg. of aureomycin daily, combined with topical applications.

3. Subconjunctival administration of chloromycetin had no effect on herpetic infection in the rabbit.

4. Terramycin borate, used topically, appeared to modify the disease in three cases of keratitis in the rabbit.

5. Aureomycin in 1.0 mg./cc. of virus suspension failed to inactivate the virus in in vitro tests, but a concentration of 4.0 mg./cc. seemed to have a definitely virustatic effect. Chloromycetin in in vitro tests failed to show any inhibiting effect.

6. Aureomycin administered orally or subcutaneously after intracerebral inoculation of mice with virus failed to prevent or to modify significantly the experimental infection. Prophylactic administration of subconjunctival aureomycin in a dose of 2.5 mg. daily effected a slightly increased survival time in mice. Large amounts of subconjunc-

tival aureomycin (5.0 mg. daily) were definitely toxic to mice.

7. Large doses of chloromycetin given orally to mice infected with the virus, with or without simultaneous reinforcement by subcutaneous injections, delayed or prevented death in two experiments. However, the same experiment repeated eight months later with the same virus failed to show significant differences between treated and untreated mice. The only difference in experimental conditions appeared to be the fact that the test virus had been passed through animals repeatedly and had apparently become more neurotropic.

8. Preliminary studies on the comparative effect of treatment with streptomycin and penicillin and with chloromycetin have been inconclusive. The possibility that increased survival times of infected mice treated with chloromycetin and aureomycin may be due to a nonspecific effect on secondary invaders seems unlikely but has not been ruled out.

9. Terramycin hydrochloride, given orally in a dose of 10 mg. per day, appeared to have no effect on infected mice.

10. None of the three antibiotics tested proved to have a truly virucidal effect on the single strain of herpes simplex virus employed in these experiments. The possibility that they may have had a mildly virustatic action was suggested but not proven.

87 North Sixth Street.

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STUDIES ON THE EFFECTS OF BETA IRRADIATION APPLIED CIRCUMFERENTIALLY TO THE CILIARY BODY OF RABBITS*

AELETA N. BARBER, PH.D., RALPH W. BRAUER, PH.D.,
AND RUDOLPH J. MUELLING, JR., M.D.
New Orleans, Louisiana

The use of beta irradiation as a possible therapeutic agent in glaucoma was first advocated by Haik, Breffeilh, and Barber in 1948.[1] The work to be reported in this paper is a continuation of that principle then reported with certain variations in technique and is a preliminary report of work which is still in progress.

It is obvious that the beneficial effects of a specific therapeutic agent will be nullified by any harmful effects, if these are present. The source of radiation used in the previous work emitted enough gamma radiation to cause cataractous changes in the lens when applied over the ciliary body of rabbits. Our aim in planning these experiments was to find a more suitable source of radiation and a feasible method of applying it to the entire circumference of the ciliary body without deleterious effects.

MATERIALS AND METHODS

1. SOURCE OF RADIATION.

Radium D+E† and phosphorus-32 were used in a preliminary series of experiments to determine their relative effectiveness. Two Swanberg Ra-D ophthalmic applicators‡ containing 10 mc. and 20 mc. respectively were used; 10 mc. of P^{32} was used in an applicator of our own design.

Radium D. Radium-D, atomic weight 210, is the disintegration product of Ra^{226}. Radium-E, the prime source of the useful beta radiation, has a half-life of only five days, but an equilibrium is soon set up, and Ra-E concentrations thereafter decrease with a half-period of 22.2 years characteristic of Ra-D. The beta rays emitted by Ra-E have a maximum energy of 1.17 mev. Polonium, or radium F, an alpha emitter, is the decay product of Ra-E.

In the Swanberg applicator the alpha rays and the soft beta rays of Ra-D are absorbed by a thin aluminum filter allowing the hard beta rays of radium E to emerge. The maximum gamma radiation is less than 0.1 percent, so that the Ra-D applicator is a source of almost pure beta radiation.

Phosphorus-32. The second source of beta radiation was 10 mc. of phosphorus-32. P^{32} emits beta rays with a maximum energy of 1.72 mev, but no gamma radiation. The half-life of P^{32} is 14.3 days; its decay product is S^{32}.

P^{32} was used exclusively in the second series of experiments. This was done in spite of the inconveniently short half-life of this isotope for the following reasons: first, P^{32} is readily available; second, this isotope is handled with relative ease and safety and can be readily introduced into the special types of applicators to be tested in this work; third, on theoretical grounds, a relatively hard beta source such as P^{32} is preferable to the softer beta rays of Ra-D because identical doses can be administered to the sensitive tissues with much smaller surface doses than in the former case.

2. METHOD OF APPLICATION

For our purpose the Swanberg applicator possessed distinct disadvantages. It was small, having a radiating window 5.6 mm. in diameter, and required numerous applications in order to irradiate the entire circumference of the ciliary body; also it was round, producing a somewhat discontinuous

* From the Departments of Pathology and Pharmacology, Louisiana State University School of Medicine, and The Charity Hospital of Louisiana.

† Referred to as Ra-D in the remainder of the paper.

‡ Loaned by Dr. W. B. Clark, Tulane University School of Medicine, New Orleans.

zone of irradiation. In order to overcome these disadvantages, we designed a ring applicator which irradiated a band 2.0-mm. wide approximately 2.0-mm. behind the limbus (fig. 1).

This applicator was constructed from an ordinary glass test tube (fig. 2). The end of the tube was heated and blown into a bulb which was then drawn inward. The concavity at the end of the tube was shaped to fit over the cornea and extended 2.0 mm. back of the limbus. It was lined with lead foil except for a 2.0 mm. ring at the outer edge. The outer walls of the test tube were shielded by a layer of lead 4.0 mm. thick. The result was an annular radioactive surface which could be placed over the anterior part of the ciliary body. (See Appendix for calibration of applicator.)

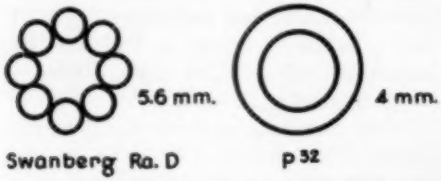

Fig. 1 (Barber, Brauer, and Muelling). Diagram showing surface contact of Ra-D and P^{32} applicators.

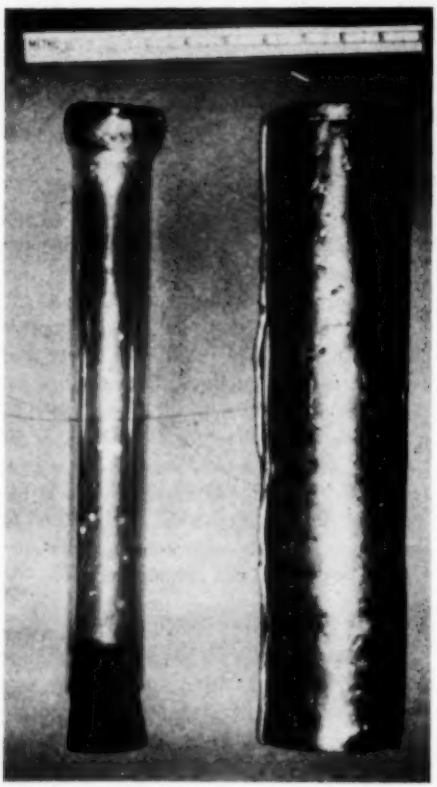

Fig. 2 (Barber, Brauer, and Muelling). P^{32} applicator and lead shielding tube.

Fig. 3 (Barber, Brauer, and Muelling). Method of applying P^{32} radiation.

The palpebral fissure of the rabbit is narrower than that of humans; thus in order to place the radioactive surface of either the Swanberg or ring applicator directly over the ciliary body, it was necessary to cut the eyelids (fig. 3). Seven or eight treatments were given with the Swanberg applicator, but the P^{32} radiation could be given in one application.

3. Target of irradiation

An average of micrometer measurements made on untreated rabbit eyes is given in Figure 4; shrinkage during preparation was estimated to be about 10 percent. The widest portion of the ciliary body exclusive of the

ciliary processes is approximately 1.2 mm. by 2.0 mm. deep, and is located about 1.5 mm. behind the limbus. This area also corresponds to the richest blood supply of the ciliary body. Reduction of this vascular bed without damage to the lens or ciliary epithelium was our objective.

Figure 5 shows that 86 percent of the P^{32} radiation is absorbed within the first 2.0 mm. of tissue; thus the ciliary body is within the range of effective penetration while the lens, which is 3.5 mm. from the surface, receives only minimal activity.* The applicator which was designed for this purpose allowed some scattering of the rays across the anterior segment of the globe (fig. 5). An applicator which confined the activity to the ciliary body in a more efficient manner is theoretically possible and might allow the use of larger doses of radiation.

4. Single applications

Preliminary experiments were planned to determine the tissue effects of five and 10

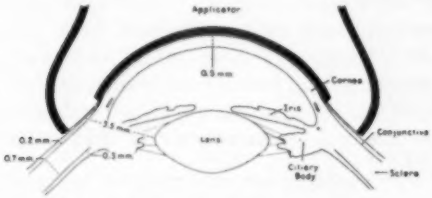

Fig. 4 (Barber, Brauer, and Muelling). Diagram of rabbit's eye.

minute irradiations with 10 and 20 mc. of radium-D and with 10 mc. of P^{32}. Because of the ease of application of the P^{32}, a 20-minute series was added in order to test the upper limits of safety for a single treatment with this applicator.

Twenty-two rabbits were used in this experiment; one eye was irradiated, the opposite eye serving as a control. The animals were killed 14, 21, 42, 90, and 180 days after this single treatment. Gross examinations of both the treated and untreated control eyes were made with an ophthalmoscope at regular intervals. There was a slight amount of redness over the ciliary body for the first three to five days after treatment but no instance of radiation burn or conjunctivitis occurred among any of the rabbits in this series.

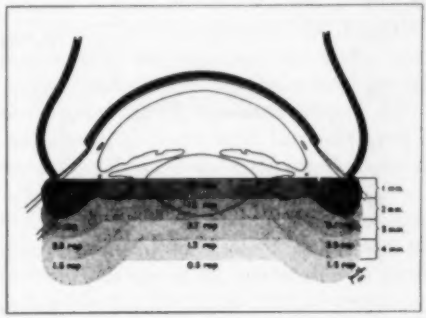

Fig. 5 (Barber, Brauer, and Muelling). Diagram of radiation field of P^{32} applicator superimposed on cross section of a typical rabbit's eye. Rep values per minute.

5. Multiple applications

A series of experiments utilizing multiple applications of P^{32} were carried out on 18 rabbits in order to test the limits of tolerance for this applicator. The first group of nine rabbits were given five and 10 minute treatments at six-week intervals for a total of three applications. (Total irradiation, 15 and 30 minutes.) The second group of animals were given treatments at two-week intervals. (Total, 30 and 40 minutes.) Two rabbits were given three 20-minute treatments at six-week intervals.

The animals were again divided into two equal groups for tonometric and fluorescein

* Surface doses administered by the several spot applications of Ra-D were without exception much higher than those administered by the use of the annular P^{32} applicator. In view of the difference in range of the two types of radiation, however, and in view of the nearly exponential absorption for beta radiation in tissue,[3] the radiation reaching the sensitive areas may actually have been larger in the case of the P^{32} applicator. This interpretation appears to be confirmed by the microscopic examination of treated eyes.

TABLE 1

SUMMARY OF RESULTS OF GROSS EXAMINATION, TONOMETRY, AND INTRAVENOUS FLUORESCEIN

Animal	P^{32} Application	Gross Measurements (mm.)	Tension (mm. Hg (Schiøtz)	Time of Fluorescein Appearance (minutes)
13		Rx* 18½×20½×20½ 19 ×21 ×21	Rx 16.9 11.9	
24	5 min. 3 times } 15 min.	Rx 18 ×19 ×19 18 ×19 ×19	Rx 23.4 27.1	
25		Rx 17½×18½×19½ 18 ×18½×19½	Rx 7.0 8.0	Rx 6½ 4½
14	5 min. 6 times } 30 min.	Rx 17½×18 ×18 19 ×20 ×20	Rx 6.2 13.2	
27		Rx 18 ×19½×20 18 ×20 ×20½	Rx 11.9 16.9	Rx 20 15
12		Rx 19 ×21 ×21 19 ×21 ×21	Rx 12.0 14.2	
34	10 min. 3 times } 30 min.	Rx 17½×19 ×18½ 18 ×19 ×19		
10		Rx 17½×19½×19½ 17½×20 ×19½	Rx 16.9 10.0	Rx 9 6
39		Rx 17 ×17 ×18 17½×18 ×18½	Rx 4.0 11.9	Rx 9 6
35	10 min. 4 times } 40 min.	Rx 17 ×18 ×18½ 17 ×19 ×18½	Rx 10.0 16.9	Rx 14 9
33		Rx 17½×20 ×21 20 ×21 ×21		
30		Rx 19 ×19½×20 19 ×21 ×21		Rx 9 4
28	20 min. 3 times } 60 min.	Rx 18½×20 ×20 18½×20½×21	Rx 6.2 10.0	Rx 12 9

* Rx = Treated eye.

studies. Those in the first group were anesthetized one month after the last application and the tension in the treated and untreated eyes was tested with a Schiøtz tonometer. These animals were killed and the eyes prepared for histologic study. The second group received intravenous injections of fluorescein and intraocular pressure was tested three months after final treatment.

Results

Results of single applications

Ciliary body. The ciliary body of all the eyes treated for five or 10 minutes with radium-D and P^{32} showed engorgement of the blood vessels and marked edema of the stroma in the animals killed 14 and 21 days after irradiation. The pigmented epithelium of the iris and ciliary body was undamaged. No essential differences could be detected between the effects of the two sources of radiation.

Sections examined 42 and 90 days after treatment showed no signs of vascular congestion or edema in the ciliary body. The blood vessels were contracted and there was an increase in fibrous tissue in the stroma. At no time was any damage to the ciliary epithelium noted.

Lens. Sections of lenses from irradiated

eyes in the five and 10 minute series of both radium-D and P^{32} showed no cataractous changes 21, 42, 90, and 180 days after treatment. The nuclei of the lens fibers were normal and in their usual anatomic arrangement.

Hydropic changes, however, were noted in the lens epithelium of the eyes of the four animals exposed for 20 minutes to P^{32} 21 days after treatment. The cells of the anterior epithelium were swollen and the epithelium was separated from the ends of the lens fibers near the equator on both sides of the lens. The condition appeared to be regressing in all the eyes of animals killed 42 and 90 days after irradiation and was not present in the animals killed six months after treatment.

Synechias between the posterior surface of the iris and the anterior surface of the lens were also present in these eyes. Since there was no damage to the pigmented epithelium of the iris or ciliary body, the condition seemed to have resulted from excessive congestion of the ciliary vessels due to prolonged irradiation rather than to direct damage by the beta rays. Thus the only deleterious effects were found in the animals irradiated for 20 minutes with P^{32} and these appeared to be transitory.

Results of multiple treatments

a. *Tension.* The intraocular pressure was reduced in all the irradiated eyes except two, No. 10 and No. 13, Table 1. In each of these eyes a dense scar approximately the size and shape of the center of the applicator was present in the center of the cornea. These probably resulted from trauma and may have been partly responsible for the failure to obtain a reduction in tension in these two eyes.

b. *Fluorescein.* A solution containing 20 mg. of sodium fluorescein per Kg. was injected into the femoral vein of six rabbits, and their eyes were observed continuously for 30 minutes and examined again at 24- and 48-hour intervals. The use of a dissecting microscope and an ultraviolet lamp did not improve upon the results obtained by direct visual observation.

The time at which the fluorescein appeared in the anterior chamber is recorded in Table 1. In every instance the fluorescein appeared in the untreated eye earlier than in the irradiated eye, but the method was not sufficiently refined to detect minute differences such as might have been expected in animals subjected to different dosages of beta irradiation.

c. *Gross measurements.* The measurements recorded in Table 1 show that the reduction in size of the irradiated eyes parallels fairly closely the number of treatments and the total amount of irradiation. This is especially marked in No. 14, No. 27, and No. 28. Reduction in size was not confined to any one meridian but was found in all planes. In no instance was the irradiated eye larger than the untreated control.

d. *Histopathology.* Celloidin and paraffin sections were stained by various special techniques including hematoxylin and van Gieson, Toluidine blue, reticulum, and the periodic acid stain as described by Hotchkiss,[3] McManus,[4] and Friedenwald.[5]

The histologic changes observed in eyes exposed to beta radiation are not as definite as those in eyes treated with radiations containing gamma rays.[1] The larger blood vessels are unaltered in size and shape. The number of capillaries in the ciliary body, however, appeared reduced in the irradiated eyes (fig. 6). The ciliary body generally seemed smaller and the stroma appeared more compact than that of the untreated eyes.

No instance of cataract formation was observed in any of the irradiated eyes.

Discussion

The postulate of the previous work[1] on this subject was based upon the assumption that a decrease in production of aqueous humor and lower intraocular pressure might follow reduction of the capillaries in the

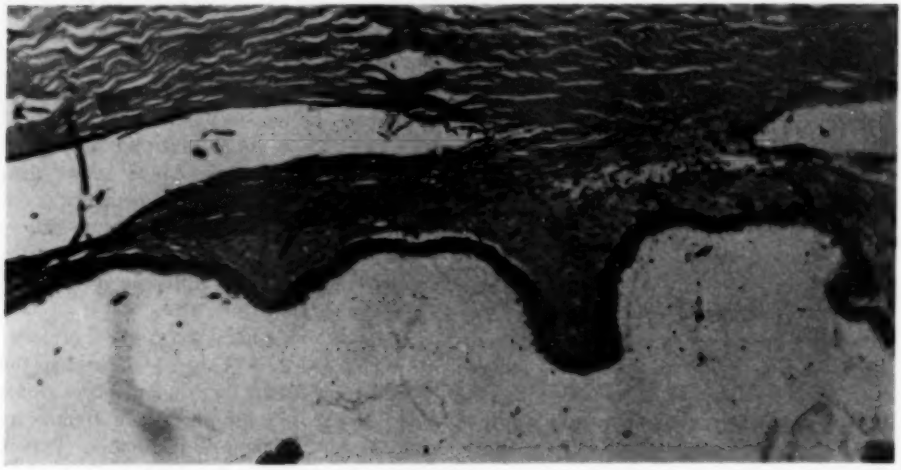

Fig. 6 (Barber, Brauer, and Muelling). Ciliary body of irradiated eye after six five-minute treatments with P^{32} applicator (30 minutes).

ciliary body, if this could be done without harmful effects.

An Iliff applicator containing 50 mg. of radium salt and emitting both beta and gamma radiations was used in that study. The treatment recommended by Iliff[6] for humans was 10 minutes and, in an earlier paper, Hughes and Iliff[7] found that rabbits could tolerate three times the dose for humans. Thus a 30-minute application should have been within the range of tolerance; however, a single 30-minute treatment over one sector of the ciliary body resulted in cataract formation and destruction of the ciliary body.

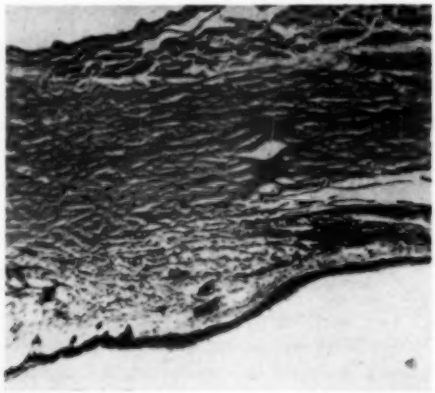

Fig. 7 (Barber, Brauer, and Muelling). Ciliary body of untreated eye.

Circumferential applications seemed a feasible method of producing a uniform effect around the entire ciliary body. The isotope, P^{32}, met all the practical requirements for an experimental type of applicator, besides having an effective range of penetration.

The methods used in evaluating the effects of the irradiation in this work possess certain limitations. Tension studies on experimental animals are notoriously difficult, but, in general, the irradiated eyes seemed softer than the untreated eyes.

Determination of the exact time at which intravenously injected fluorescein can first be detected in the anterior chamber is also a difficult procedure. Gifford,[8] Haefeli,[9] Stocker,[10] and others have used this method as a means of studying intraocular pressure and permeability of the blood-aqueous barrier. They found that the time of appearance and its concentration in the anterior chamber depend, among other factors, largely on the state of capillary permeability in the iris and

ciliary body, and any increase in capillary permeability would accelerate the rate of appearance and its concentration in the aqueous. The finding of delayed appearance of fluorescein in the eyes treated with beta irradiation is consistent with a decrease in capillary permeability or total vascularity.

Histologic study of the tissues following beta irradiation fails to reveal any direct effect upon vascular endothelium similar to that which is classically described following exposure to gamma rays. Instead the end result appears to be an increase in the compactness of the stroma with obliteration of some of the capillaries.

These findings confirm those of Rhoades[11] following beta irradiation in other parts of the body. The transient edema followed by loss of stromal cells is consistent with the observations of Wilson,[12] and Hughes and Iliff[13] on the cornea and conjunctiva.

Summary

1. Beta radiation in the amount of 10 mc. of P^{32} was applied circumferentially to the ciliary body of rabbits for three to six times during a period of three months. The period of each application varied from five minutes to 10 minutes and the total time of application was from 15 minutes to 40 minutes.

2. In none of the rabbits was there any gross or microscopic evidence of cataract formation.

3. Evidence obtained through physiologic methods (tonometry and fluorescein) points toward a reduction of intraocular pressure and a decrease in vascularity (or permeability), respectively.

4. Evidence obtained from anatomic methods (gross measurements and histologic study) was somewhat disappointing, but in general supported a reduction in the size of the eye and a decrease in vascularity with a decrease in size and an increase in compactness of the ciliary body.

5. The evidence from all sources points toward further exploration of beta radiation as a possible therapeutic tool in the treatment of glaucoma.

Louisiana State University
Medical Center.

Appendix A

The applicator was calibrated using dental X-ray film, essentially according to the procedure of L. E. Glendenin.[14] The only modification to the method thus described was that the film was exposed either in direct contact with the applicator, or separated from the applicator by one or more thicknesses of spent film which served as a filter of specified mass thickness and composition approaching that of tissue.

From the film darking, the dosages were estimated visually by comparison with film exposed to known amounts of gamma radiation from a filtered 5.0-mg. radium source. While the rep values thus obtained are inaccurate due to differences in film sensitivity to the various radiations, the values are readily reproducible.

The radiation field obtained in rep per minute is shown in Figure 1, where it is superimposed on a cross section of a typical rabbit's eye.

We wish to acknowledge the assistance of Mr. John S. Krebs in the calibration of the P^{32} applicator.

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SEPARATION OF THE PARS CILIARIS RETINAE IN RETROLENTAL FIBROPLASIA*

JOSEPH M. DIXON, M.D.
Birmingham, Alabama

AND

ELEANOR V. PAUL, M.S.
Washington, D.C.

Retrolental fibroplasia is a term applied by Terry[1] to ocular maldevelopment appearing during the first half year of life in infants born prematurely and occasionally in full-term infants. The term does not describe the lesion accurately, but no appropriate substitute has been suggested.

There has been considerable difference of opinion concerning the pathogenesis of this lesion,[2-13] probably because the emphasis has been on clinical rather than pathologic considerations. A thorough understanding of the pathologic changes which characterize retrolental fibroplasia should serve to resolve these conflicts, but to date only scattered reports on the pathologic aspects have been published.

It is the purpose of this paper to present detailed descriptions of the histopathologic features of retrolental fibroplasia as seen in 11 cases (one eye from each) at the Armed Forces Institute of Pathology, to correlate these observations with the clinical data, and to offer an explanation of the lesion on the basis of normal embryologic development rather than on anomalous development.

To obtain this material, 13 cases previously recorded as possible retrolental fibroplasia were examined. Since retrolental fibroplasia has only recently been adopted as a diagnostic category, and thus it was probable that additional cases might be included in other categories, more than 50 cases of congenital anomaly and pseudoglioma were also reviewed.

Furthermore, both normal eyes of 20

* From Armed Forces Institute of Pathology and the Department of Ophthalmology, Medical School, University of Cincinnati, Cincinnati, Ohio.

Since this paper was presented, Eugene Wolff has published (Am. J. Ophth., **33**:1768-1774, 1950) observations of separation of the pars ciliaris retinae which agree with ours.

premature and 10 full-term infants were studied and the resulting data suggested that factors which interfere with development may prevent the normal adherence between the two layers of the optic cup. A review of the embryologic development of the tissues involved in retrolental fibroplasia will contribute to an understanding of its pathologic features.

Embryologic and anatomic factors

As the primary optic vesicle invaginates to form the optic cup the retinal pigment epithelium arises from the outer wall and the rest of the retina from the inner wall. The margin of the optic cup grows forward to form the epithelium of the ciliary body (pars ciliaris retinae). The two layers of the optic cup do not develop at the same rate. Even in the adult these layers do not have anatomic continuity and their cohesion is relatively loose. Meanwhile the pars optica retinae is developing and undergoing differentiation into its various layers.

The ora serrata in the partially developed eye lies over the belly of the ciliary muscle (fig. 1) since the pars plana is not completely formed before the eighth month.[14] The position of the ora serrata in a normal full-term infant is at or behind the posterior border of the pars plana (fig. 2).

It is doubtful if this more posterior position of the differentiated retina represents an atrophy of the anterior portion of the retina; it is more likely a result of growth and differentiation of the ciliary body and its pars plana. The premature infant is born with this differentiation yet to be completed.

Fig. 1 (Dixon and Paul). Ora serrata at level of belly of ciliary muscle in premature infant (22 weeks' gestation). (AFIP Acc. 195500.)

Fig. 2 (Dixon and Paul). Ora serrata at posterior border of fully developed pars plana in full-term infant at birth. (AFIP Acc. 196270.)

The zonular fibers at their ciliary ends are attached to the ciliary epithelial cells from which, theoretically, the fibers arise as processes. The cuticular lamina of the ciliary body in the fully differentiated eye has an irregular surface arranged in ridges and thus furnishes a firm attachment for the layer of pigment epithelial cells and prevents their separation by traction of the zonular fibers.[15] A cementing substance causes these cells to adhere to the cuticular lamina, to each other, and to the pars ciliaris.

It is not known at what point in fetal development the cementing substance which assists in preventing the separation of the pars ciliaris is first elaborated, but it is logical to believe that it is late, because the structures in this region are not completed until the pars plana is fully formed.

The larger and more numerous zonular fibers are attached to the pars ciliaris only 1.5 mm. anterior to the ora serrata; however, the entire surface of the ciliary body, with the exception of the tips of the processes, furnishes support to these fibers.[15] Thus the pars ciliaris has the burden of sup-

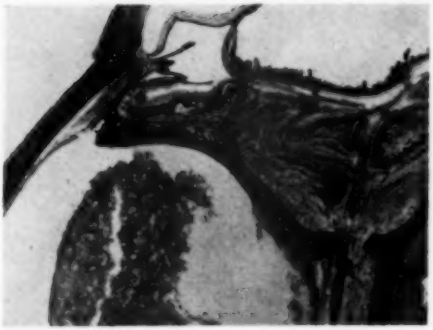

Fig. 3 (Dixon and Paul). Separated pars ciliaris retinae and pars optica retinae in retrolental fibroplasia. Gliosis of retina. (AFIP Acc. 187981.)

porting the lens by means of the zonular fibers.

It should not be surprising, therefore, that the poorly closed space of the primary optic vesicle should separate in premature infants, especially if the pull on this structure were increased by movements of the ciliary muscle.

Clinical data

In this series of 11 cases the clinical records were consistent with the concept that retrolental fibroplasia occurs most frequently in prematurity. Birth weights were listed in seven of the cases. Six of the infants weighed 3.5 pounds or less, the seventh, 4.5 pounds. Weight was not recorded in four cases, but one of these infants was born in the sixth month of fetal life, and two were members of twin births, which suggests that weight was well within the range of prematurity. The other infant was born at full term.

Since all but one of the eyes were enucleated for suspected retinoblastoma, none was studied clinically for the development of retrolental fibroplasia. Onset was recorded in only four cases: at 3, 3.5, and 4 months in premature infants and at one month in the full-term infant.

Seven of the premature infants were six months of age or younger at the time of enucleation; two were more than six months, and only one was older than a year. The full-term infant was two months old when the eye was removed. In seven of the premature infants, the condition was known to be bilateral, in one it was apparently unilateral, and for the remaining two complete data were not available. The clinical history of the full-term infant indicates that retrolental fibroplasia may have been bilateral.

Measurements were available on six of the enucleated eyes and the average dimensions were 19.6 by 18.5 by 17.6 mm.

Pathologic observations

The separation of the nonpigmented ciliary epithelium apparently began near the ora serrata. This layer became folded forward to form a double-layered epithelial

Fig. 4 (Dixon and Paul). Higher power of area from Figure 3. Folding of pars ciliaris retinae.

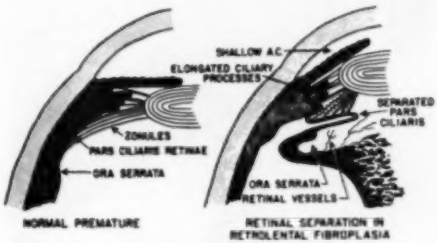

Fig. 4-a (Dixon and Paul). Diagram of separated retina and pars ciliaris with shallow anterior chamber. Possible mechanism of elongation of ciliary processes by traction of zonules.

fold. In addition to the mechanical folding there was evidence of proliferation of the cells. The pars optica retinae took part in this separation and remained attached to the separated pars ciliaris (figs. 3 and 4).

Since the largest and most numerous zonular fibers are attached to the ciliary epithelial cells near the ora serrata, the separation of this layer of cells destroyed the posterior support of the lens in most of the cases, allowing it to be displaced forward to form a shallow anterior chamber. Thus only the zonular fibers arising anteriorly from the corona remained to support the lens.

The underlying pigment epithelial layer of the ciliary body proliferated profusely along the posterior surface of the separated retina,

Fig. 5 (Dixon and Paul). Elongation of ciliary processes and proliferation of ciliary pigment epithelium along the posterior surface of the separated retina. (×45. AFIP Acc. 187981.)

as illustrated in Figure 5, and in one case reached almost as far as the optic disc.

New vessels from the vascular layer of the ciliary body at the level of the ora serrata proliferated into the subretinal space along with the pigment epithelium and were probably the source of the subretinal hemorrhages (figs. 6 and 7). The increased number of new vessels in areas of hemorrhage represented the usual pathologic process of organization of damaged tissue. The retinal pigment epithelium did not take part in this proliferation.

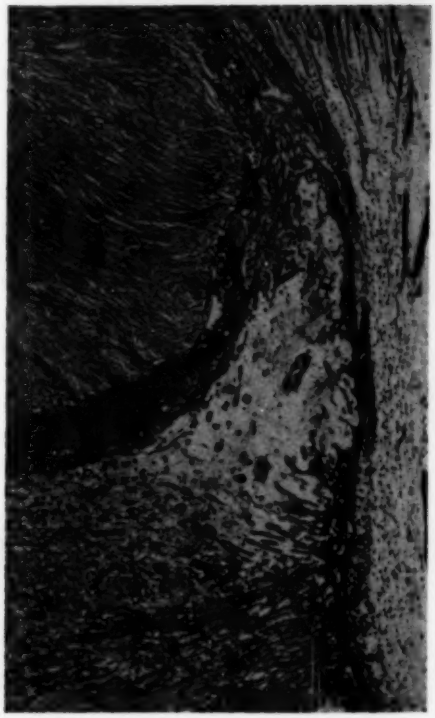

Fig. 6 (Dixon and Paul). Proliferated ciliary pigment epithelium in subretinal vascular membrane. (×62. AFIP 212354.)

When separation of the pars ciliaris was incomplete, the nonpigmented ciliary epithelial cells anterior to the point of separation proliferated along their attached zonular fibers and contributed to the retrolental membrane (figs. 8 and 9). Proliferation of the underlying pigment epithelium was minimal, while it was prominent in the nonpigmented epithelium anterior to the separation.

In the specimens examined, the pars optica retinae was completely detached in a funnel-shaped type of separation and had undergone gliosis (fig. 3). In some cases rosettes had formed in the retina, especially in eyes from the most premature of the infants where differentiation was not far advanced (figs. 5 and 10). Proliferation of the

Fig. 7 (Dixon and Paul). Vessel derived from ciliary body growing beneath the retina. Proliferated ciliary epithelium. Higher power of Figure 6. (×145.)

Fig. 8 (Dixon and Paul). Proliferation of nonpigmented ciliary epithelium along zonular fibers anterior to partially separated pars ciliaris. (AFIP Acc. 94723.)

retinal vascular endothelium formed solid cords of cells scattered throughout the separated retina.

Any defects of the lens were secondary, and the presence of nucleated epithelial cells beneath the posterior lens capsule was not prominent as in developmental anomalies. Rupture of the lens capsule and invasion of the lens by hyperplastic primary vitreous were not seen. Calcium was observed in the lens in three cases.

Retrolentally, in addition to the separated, gliosed retina, there were varying amounts of fibroblasts and thin-walled vessels contributed by the retina, and sometimes layers

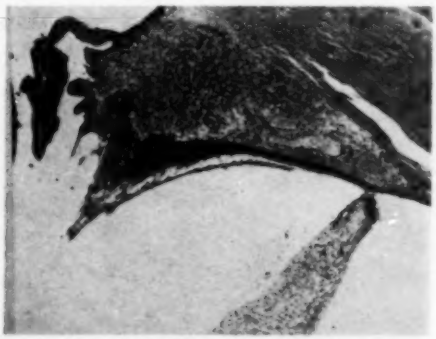

Fig. 9 (Dixon and Paul). Proliferation of both pigmented and nonpigmented ciliary epithelium anterior to separated retina. (AFIP Acc. 51492.)

of condensed secondary vitreous (figs. 3, 10, and 11). Separation, folding, and proliferation of the nonpigmented ciliary epithelium, alone or in various combinations, were seen in every case, and occasionally extended to the posterior margin of the lens.

In the sections examined no evidence was seen of a persistent hyaloid artery or of hyperplasia of the tunica vasculosa lentis. Evidence of inflammation was lacking in eight of the eyes. In the other three, it was slight, being limited to plasma cells in the iris in one case and in the ciliary body in another, and to a few lymphocytes in the retrolental membrane in a third. The presence of so small an amount of inflammation

was regarded as a secondary manifestation.

Pathologic changes resulting from separation of the pars ciliaris were not identical in the specimens studied. In four, the vessels from the ciliary body did not proliferate into the subretinal space and instead of subretinal hemorrhage there was serous eosinophilic exudate. In these same eyes pigment proliferation along the posterior surface of the separated retina was absent or minimal, and the pars ciliaris retinae was separated usually on only one side of the globe.

Correlation of Clinical and Pathologic Pictures

With minor exceptions, the pathologic observations confirmed the clinical data. The

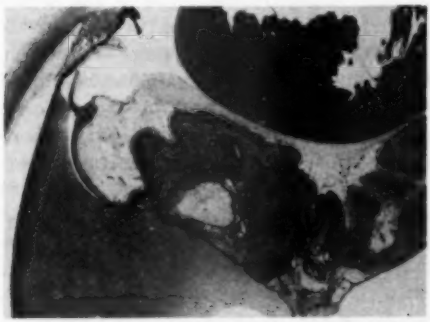

Fig. 10 (Dixon and Paul). Retrolental mass composed of separated retina with rosettes, a thin fibrovascular membrane on its inner surface, and condensed secondary vitreous immediately behind the lens. (×14. AFIP Acc. 94723.)

folded, white, vascularized, retrolental membrane seen clinically in the region of the ciliary body was identified in the enucleated eyes as the separated retina with its vessels.

The early retinal edema and dilated retinal vessels seen ophthalmoscopically are transient changes and could not be confirmed pathologically because the eyes were enucleated at a later date. However, it is believed that these changes could be a manifestation of an earlier lesion in the region of the ora serrata, which is not usually visible clinically.

The retinal exudates observed ophthalmoscopically were not found in the specimens in this study.

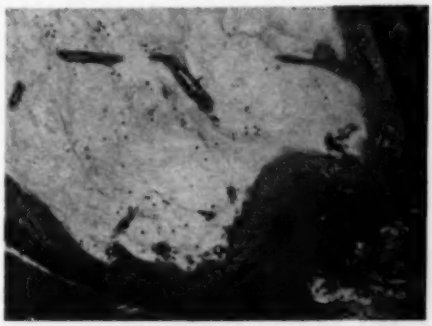

Fig. 11 (Dixon and Paul). New vessels leaving retina. (×100. AFIP Acc. 94723.)

The hemorrhages, elongated ciliary processes, usually normal lens, and shallow anterior chamber were all confirmed pathologically. Elongation of the ciliary processes, however, was less pronounced than on ophthalmoscopic examination, possibly because the anterior displacement of the lens exposing the processes made them appear longer than they actually were. Developmental abnormalities and remnants of the hyaloid artery, tunica vasculosa, and other fetal structures were not observed pathologically in this series.

The sizes of the eyes in this group were within the normal limits for infants during the first year of life, the normal individual variation being wide. However, conclusions as to microphthalmos could not be based on so small a series. The apparent smallness of the eyes noticed clinically is perhaps the result of failure of ocular growth after the retinal separation begins.

Comment

The causes of premature birth are numerous and can be divided into two general groups:[16] Those resulting in the premature expulsion of a normal fetus, and those which damage the product of conception.

The normal fetus subjected to the misfortune of premature birth has many in-

Fig. 12 (Dixon and Paul). Persistence and hyperplasia of primary vitreous with elongation of incarcerated ciliary processes in hyperplastic tissue. The pars optica retinae has also been incarcerated and has been separated behind the ora serrata without involvment of the pars ciliaris. (×27. AFIP Acc. 88042.)

completely differentiated organs and tissues and is poorly prepared for extrauterine existence. One of the most serious difficulties with which the premature infant has to contend is hemorrhage,[17] which in this series was present in seven of the 11 eyes. It can be explained on the basis of the fragility of blood vessels and frequent low blood prothrombin in premature infants. The organization of the hemorrhages by new vessels and fibroblasts was more often beneath the retina than in the retinal funnel and was not regarded as a mechanism of retrolental fibroplasia.

All of the specimens, including serial sections from two eyes, were searched for embryonic or hyperplastic tissue resembling tunica vasculosa lentis and hyaloid artery, but neither were identified. Except in normal locations no vascular tissue was found other than that arising from the ciliary body and extending subretinally and that which contributed to the retrolental membrane, involving the inner retinal surface.

In the first instance the subretinal granulation tissue was regarded as organization of subretinal hemorrhage and a reaction to damaged tissue. In the second instance the absence of a patent hyaloid artery, which is the normal source of the vessels of the primary vitreous, led to the conclusion that the vessels were derived from the separated retina rather than from the hyaloid system.

For comparison, 35 cases of persistence and hyperplasia of the primary vitreous were examined. In this condition the normal embryonic retrolental tissue persists and undergoes hyperplasia and fibrosis and, in some instances, incarcerates the rim of the optic cup.

During growth the anterior border of the retina remains adherent to the vascular tissue. In these cases separation of the pars optica is regarded as a true detachment resulting from traction of the hyperplastic membrane. The pars ciliaris remains in situ. In other instances the retina is not incarcerated and is not detached.

Elongation of the ciliary processes is much less prominent in retrolental fibroplasia than in congenital hyperplasia of the primary vitreous where the processes become adherent to this tissue during the early fetal

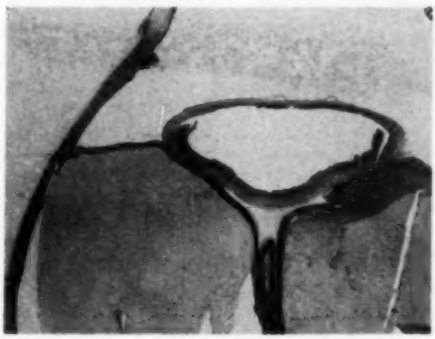

Fig. 13 (Dixon and Paul). Idiopathic separation of the retina in a two-year-old child, without involvement of the ciliary body and with retinal degeneration rather than active tissue proliferation. (×10. AFIP Acc. 183023.)

months when they are normally in contact with the lens. Compare Figure 12 with Figures 3 and 10.

The presence of retrolental fibroplasia in one infant born at full term is interesting.

In this case the lesion was first noticed by the parents when the child was one-month old, and it is likely that it was present or had started at the time of birth.

Either of two factors could have been responsible: partial persistence of the primary optic vesicle in the region of the ciliary body with incomplete approximation of the pars ciliaris, or delay in development of the eye as a whole so that it did not keep pace with that of other organs. In the latter event the conditions at birth in a full-term infant would be the same as those in the eye of a premature infant.

In idiopathic separation of the retina in otherwise normal full-term infants, the separation does not extend anterior to the ora serrata and the ciliary body is not involved (fig. 13).

There is a conspicuous contrast between the reaction to retinal separation in the mature, fully differentiated eye and in the eye of the premature infant. In the former, only the pars optica is involved and degenerative changes in this structure follow. Separation of the pars ciliaris retinae in the adult is seldom seen pathologically and even more rarely clinically. Klien[18] described this condition in a few cases of malignant melanoma of the uveal tract and in cases of violent trauma. It is also seen occasionally in the presence of severe inflammatory reactions.

Retinal separation in the premature infant is followed by proliferation of ciliary pigment epithelium and new vessels, the formation of rosettes, and the binding together of this mass by the retinal glia into a firm retrolental disc.

To understand the mechanism of the initial separation of the pars ciliaris retinae we must consider the fetal position of the ora serrata over the ciliary muscle, the traction of the zonular fibers on the pars ciliaris, and the failure of the cement substance to prevent this separation. Also to be taken into account is the possibility that the separation might be spontaneous or initiated by shrinking of the anterior vitreous. Such considerations need not exclude metabolic factors or vascular changes as the initial etiology.

Summary

In a review of pathologic material at the Armed Forces Institute of Pathology, 11 cases of retrolental fibroplasia were found, 10 in premature infants and one in a full-term infant. The pathologic changes were separation of pars optica retinae and pars ciliaris retinae with its attached zonular fibers. The lens lost its posterior support and shifted forward.

New vessels from the vascular layer of the ciliary body proliferated beneath the retina, and in some cases there was evidence of subretinal hemorrhage. Proliferation of the ciliary pigment epithelium was a secondary manifestation.

The retrolental membrane consisted primarily of separated pars ciliaris retinae and pars optica retinae, the latter contributing varying amounts of fibroblasts and thin-walled vessels to the retrolental region.

Developmental defects and remnants of the hyaloid artery and tunica vasculosa lentis were not observed.

The fact that some degree of separation of the pars ciliaris retinae was seen consistently in the present series, although it is seldom encountered in other pathologic conditions even in the eyes of infants, may indicate that developmental immaturity is an important factor in retrolental fibroplasia.

903 South 21st Street.

7th Street and Independence Avenue, S.W. (25)

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Ohio; U. S. Naval Hospital, Sampson, New York; Dr. George B. Werner, Binghamton, New York.

Since preparation of this study, one of us (J. M. D.) through the courtesy of Dr. Parker Heath had the opportunity to study the postmortem eyes of an earlier case. The onset of the lesions had been observed clinically and, in both of the enucleated eyes, there was an early separation of the pars optica retinae near the ora serrata and proliferation of the peripheral retinal vessels into the vitreous had started before separation of the pars ciliaris began.

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NINETEENTH MEETING

of the

Association for Research in Ophthalmology, Inc.

Proceedings

Business Session

Auditors' Report

Directory of Members

Geographical List

New Members

PUBLICATIONS COMMITTEE

PHILLIPS THYGESON, *chairman*
San Jose, California

JAMES H. ALLEN, *New Orleans, Louisiana*

KENNETH C. SWAN, *Portland, Oregon*

Advisory Members

DERRICK VAIL, *Chicago, Illinois*

FRANCIS HEED ADLER, *Philadelphia, Pennsylvania*

CONRAD BERENS, *New York, New York*

San Francisco, California
June 24 and 25, 1950

OFFICERS OF THE ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.
1950

Trustees

Walter H. Fink, M.D. ..... Minneapolis, Minnesota
Kenneth C. Swan, M.D. ..... Portland, Oregon
David G. Cogan, M.D. ..... Boston, Massachusetts
Brittain F. Payne, M.D. ..... New York, New York
P. Robb McDonald, M.D. ..... Philadelphia, Pennsylvania
William F. Hughes, Jr., M.D. ..... Chicago, Illinois

Secretary-Treasurer

James H. Allen, M.D. ..... New Orleans, Louisiana

Section Secretaries

Canada
Clement McCulloch, M.D. ..... Toronto, Canada

Central and South America
Moacyr E. Alvaro, M.D. ..... São Paulo, Brazil

United States

Eastern Section
Hunter H. Romaine, M.D. ..... New York, New York

Midwestern Section
T. E. Sanders, M.D. ..... St. Louis, Missouri

East Central Section
Charles K. W. Ascher, M.D. ..... Cincinnati, Ohio

Western Section
Michael J. Hogan M.D. ..... San Francisco, California

Southern Section
Alston Callahan, M.D. ..... Birmingham, Alabama

Committee on Admissions

Parker Heath, M.D. ..... Boston, Massachusetts
Daniel B. Kirby, M.D. ..... New York, New York
Dohrmann K. Pischel, M.D. ..... San Francisco, California

Program Committee

S. Rodman Irvine, M.D. ..... Beverly Hills, California
W. Morton Grant, M.D. ..... Boston, Massachusetts
Derrick Vail, M.D. ..... Chicago, Illinois

Committee on Local Arrangements

Michael J. Hogan, M.D., *chairman*

Frederick C. Cordes W. E. Borley

BUSINESS SESSION

Saturday afternoon, June 24, 1950

The business session of the Association for Research in Ophthalmology, Inc., convened at 2:00 o'clock in Toland Amphitheater, University of California Medical School, San Francisco, California, with Dr. Walter H. Fink presiding.

DR. WALTER H. FINK (chairman): I should like to call the meeting to order and begin our business session, which will be very brief.

At the trustees' meeting last night it was decided to appoint a council on public relations, which would handle the release of information relative to the programs of the association to the press. This committee will coöperate with other similar committees in other organizations; the committee will be announced at a later time.

We would like to have the report of the secretary-treasurer.

DR. JAMES H. ALLEN: Substitute auditor's report, which follows.

CHAIRMAN FINK: May we have the report of the auditing committee?

DR. WILLIAM F. HUGHES, JR.: The finances of the society have been carefully gone over by professionals, the firm of McGladney, Hansen, Dunn and Company, of Iowa, and the report seems to be in very fine order.

CHAIRMAN FINK: Thank you. Next, the committee on publications.

DR. ALLEN: Mr. Chairman, I wish to report for the publications committee that, during the course of the year, Dr. Derrick Vail has made the offer of publishing the *Proceedings* of the Association for Research in Ophthalmology as a supplement to the AMERICAN JOURNAL OF OPHTHALMOLOGY, to be distributed to the membership of this organization and to all other subscribers of the AMERICAN JOURNAL OF OPHTHALMOLOGY for a total cost of $1,000 per year to the organization. I believe you will recall that when we attempted this once before, it cost the society between $2,500 and $3,000. This represents no reduction in the printing cost whatsoever but an increase in the amount of support that the AMERICAN JOURNAL OF OPHTHALMOLOGY is willing to give to the publication of the proceedings of this society.

The trustees, at their meeting, voted approval of this action, and, subject to the approval of the society, we will proceed with the publication of the *Proceedings* of the association as a supplement to the AMERICAN JOURNAL OF OPHTHALMOLOGY annually on that basis.

In addition, the publications committee feels that it might be advisable for the secretary to issue a news bulletin in the form of a mimeographed letter which may be mailed at a pound rate and cost the society relatively little for mailing and postage expenses, but mail these news bulletins at irregular intervals as the occasion demands. If the society approves, this can be done without a great deal of additional expense to the society at the present time.

CHAIRMAN FINK: I should like to ask the question as to whether or not the association approves of these moves: first of all, the publication of the *Proceedings* for $1,000; and then these periodic letters. Have I any expressions? Do I hear a motion that these recommendations be accepted?

(Upon motion by Dr. Harold F. Falls, seconded by Dr. A. E. Maumenee, and carried, the recommendations of the publications committee were accepted.)

CHAIRMAN FINK: The next order of business is the report of the nominating committee.

DR. KENNETH C. SWAN: The committee consists of Dr. McGavic, Dr. McGuire, and Dr. Sanders, who are unable to attend and have sent these letters:

"We believe that the trustee should be from the Deep South, in active research, and

someone who can stimulate research in that area. We believe that Dr. William B. Clark will more than meet those requirements."

The nominating committee presents the name of Dr. James H. Allen of New Orleans, as the nominee for secretary-treasurer, and makes the following statement: "The committee believes that the secretary-treasurer should be commended on the effective manner in which he has carried out the difficult duties of his office in his previous terms. Through his efforts the activities of this organization have reached a new height of excellence and efficiency. We believe he deserves the thanks of the association (as well as renomination)."

They have recommended Dr. William B. Clark as the new trustee and Dr. James H. Allen to continue as secretary-treasurer.

CHAIRMAN FINK: Thank you. Are there any other suggestions or nominations? Do I hear a motion?

DR. PHILIP R. MCDONALD: I move the election of the nominees presented by the committee.

(The motion was seconded and carried and Dr. William B. Clark was elected trustee; Dr. James H. Allen, secretary-treasurer.)

CHAIRMAN FINK: I believe that concludes the business phase of the meeting, so we can start on the afternoon papers.

AUDITORS' REPORT

Association for Research in Ophthalmology, Inc.

Pursuant to your request, we have examined the accounting records of the secretary-treasurer of the Association for Research in Ophthalmology, Inc., Iowa City, Iowa, for the year ended December 31, 1949. We submit as our report the statements listed in the following exhibits, together with related comments:

EXHIBIT A: Statement of Cash and Securities as of December 31, 1949.

Schedule A-1: Changes in the Proctor Medal Fund for the year ended December 31, 1949.

EXHIBIT B: Statement of Cash Receipts and Disbursements for the year ended December 31, 1949.

EXHIBIT C: Reconciliation of 1949 dues with the number of members for the year ended December 31, 1949.

EXHIBIT D: Analysis of changes in membership for the year ended December 31, 1949.

EXHIBIT E: Statement of Membership as of December 31, 1949.

Scope of examination

Cash receipts as recorded in the cash receipts book were traced to the bank deposits and to the individual member cards. The cash received was reconciled to the total number of members shown on the official list of members which is to be published. Disbursements were verified by examination of paid checks and available supporting invoices and other data. All disbursements appeared to be proper. Cash in bank was reconciled to the amount reported to us by the depository. The cash on hand was counted, and the U. S. Treasury bonds were inspected.

Only those members who have paid dues for the year 1949 are included in the membership for the year 1949 as shown on *Exhibit E.* A total of 43 members who were included in the membership of 1948 have not been considered as members at December 31, 1949, because of nonpayment of dues.

Accountants' opinion

In our opinion, the accompanying statements of cash and securities and cash receipts and disbursements fairly present the fund balances of the Association for Research in Ophthalmology, Inc., Iowa City, Iowa, at December 31, 1949, and the total receipts and disbursements of the association for the year then ended.

Respectfully submitted,
McGladrey, Hansen, Dunn, and Company.
Iowa City, Iowa.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

EXHIBIT A

STATEMENT OF CASH AND SECURITIES

December 31, 1949

Assets		
Cash: on Hand	$ 19.00	
First National Bank, Iowa City, Iowa	7,386.84	
Total Cash (Exhibit "B")		$ 7,405.84
U. S. Treasury Bonds—2½%, 1967-72 (At Cost)		4,099.84
Total Assets		$11,505.68
Net Worth		
General Fund	$ 1,305.68	
Proctor Medal Fund (Schedule A-1)	10,200.00	
Total Net Worth		$11,505.68

SCHEDULE A-1

CHANGES IN PROCTOR MEDAL FUND

December 31, 1949

Balance—December 31, 1948		$ 4,211.37
Less: Interest Income Credited to the Proctor Medal Fund in Prior Years Transferred to the General Fund		211.37
Adjusted Balance—December 31, 1948		$ 4,000.00
Add: Gift from Mrs. Elizabeth C. Proctor for Proctor Medal Fund		6,200.00
Balance—December 31, 1949 (Exhibit "A")		$10,200.00

EXHIBIT B

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

Year ended December 31, 1949

CASH RECEIPTS:			
1948 Dues:			
8 Active Members at $5.00		$ 40.00	
1949 Dues (Exhibit "C"):			
21 Sustaining Members at $25.00	$ 525.00		
392 Active Members at $5.00	1,960.00		
50 Educational Members at $2.00	100.00	2,585.00	
1950 Dues:			
3 Active Members at $5.00	$ 15.00		
1 Educational Member at $2.00	2.00	17.00	
TOTAL DUES		$2,642.00	
Gift from Mrs. Elizabeth C. Proctor for Proctor Medal Fund		6,200.00	
Bond Interest		50.00	
Banquet		820.00	
TOTAL CASH RECEIPTS			$9,712.00
CASH DISBURSEMENTS:			
Bookkeeper's Salary		$ 240.60	
Convention Expense:			
Luncheons and Dinner	$ 816.20		
Programs	192.95		
Reporting Meeting	152.64		
Expenses of Secretary-Treasurer	100.00		
Photo Service	25.00	1,286.79	
June Supplement to the American Journal of Ophthalmology—Share of Cost		2,542.19	
Proctor Medal Expense		710.90	
Stationery, Supplies, Printing and Postage		161.27	
Secretarial Service		60.00	
Auditing		55.00	
Premium—$5,000.00 Position Bond—Secretary-Treasurer		25.00	
Safety Deposit Box Rental (Two Years)		7.20	
Long Distance Telephone and Telegrams		6.48	
Social Security Tax		3.00	
TOTAL CASH DISBURSEMENTS			5,098.43
EXCESS OF CASH RECEIPTS OVER CASH DISBURSEMENTS			$4,613.57
CASH BALANCE—*December 31, 1948*			2,792.27
CASH BALANCE—*December 31, 1949* (EXHIBIT A)			$7,405.84

EXHIBIT C

RECONCILIATION OF 1949 DUES RECEIVED WITH NUMBER OF MEMBERS

Year Ended December 31, 1949

Membership at December 31, 1949 (Exhibit "D")		474
Add:		
Dues Received from Member Who Became Honorary Member During Year		1
TOTAL		475
Less:		
Honorary Members	11	
Life Member	1	12
Number of Members Who Paid 1949 Dues		463

1949 Dues Received (Exhibit B):	
21 Sustaining Members at $25.00	$ 525.00
392 Active Members at $5.00	1,960.00
50 Educational Members at $2.00	100.00
463 (As Above)	$2,585.00

EXHIBIT D

ANALYSIS OF CHANGES IN MEMBERSHIP

Year Ended December 31, 1949

Membership at December 31, 1948		422
Add:		
New Members Admitted in 1949	97	
Applicants Approved for Membership in 1948 Not Included in Membership Until 1949 When Dues Were Paid	4	101
TOTAL		523
Deduct:		
Deceased	4	
Resigned	2	
Members Who Were Included in Membership At December 31, 1948 Who Have Not Paid 1949 Dues	43	49
Members at December 31, 1949 (Exhibit C)		474

EXHIBIT E

STATEMENT OF MEMBERSHIP

December 31, 1949

SUMMARY OF MEMBERS:	
Sustaining	21
Active	391
Educational	50
Honorary	11
Life	1
TOTAL MEMBERS	474

MEMBERS BY YEARS	
1949	474
1948	422
1947	306
1946	324
1945	Not Available
1944	283
1943	Not Available
1942	281
1941	279
1940	270
1939	268
1938	272
1937	249
1936	240
1935	245
1934	230
1933	219
1932	203
1931	193
1930	134

NOTE: The membership for 1949 includes only those members who have paid 1949 dues. There were 43 members included in the membership of 1948 who have not been considered as members at December 31, 1949, because of nonpayment of dues.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

1950

Honorary Members

de Andrade, Cesario, Bahia, Brazil
Beach, S. Judd, Portland, Me.
Berens, Conrad, New York, N.Y.
Duke-Elder, Lady Phyllis, London, England
Duke-Elder, Sir Stewart, London, England
Ferrer, Horatio, Havana, Cuba
Lancaster, Walter B., Boston, Mass.
Parker, Walter R., Detroit, Mich.
Paton, Leslie, London, England
Zentmayer, William, Philadelphia, Pa.

Life Member

Rutherford, Cyrus W., Indianapolis, Ind.

Sustaining Members

Allen, James H., New Orleans, La.
Benedict, William L., Rochester, Minn.
Chamberlain, Webb P., Jr., Cleveland, Ohio
Cutler, Morton, Twin Falls, Idaho
Dunnington, John H., New York, N.Y.
Fonda, G. E., Millburn, N.J.
Hartenbower, G. E., Bloomington, Ill.
Johnson, Lorand V., Cleveland, Ohio
Key, Samuel N., Jr., Austin, Tex.
Last, Murray A., New York, N.Y.
LeWin, Thurber, Buffalo, N.Y.
Marshall, M. R., Edmonton, Alberta, Canada
Matthews, John L., San Antonio, Tex.
Mesirow, M. E., Santa Maria, Calif.
Ohly, John H., Brooklyn, N.Y.
Payne, Brittain F., New York, N.Y.
Reese, Algernon B., New York, N.Y.
de Roetth, Andrew F. M., Spokane, Wash.
Ruedemann, A. D., Detroit, Mich.
Smith, E. Terry, West Hartford, Conn.
Thomas, Harry V., Clarksburg, W.Va.
Thorpe, Harvey E., Pittsburgh, Pa.
Thygeson, Phillips, San Jose, Calif.
Yudkin, Arthur M., New Haven, Conn.

Deceased

Friedenwald, Harry
Dewey, C. H.
Gradle, Harry S.
Buffington, W. R.
Buschke, Wilhelm

Resigned

Sachs, Erich

Members

A

Abraham, S. V., 6363 Wilshire Blvd., Los Angeles 36, Calif.
Abrams, Henry, 195 Nassau St., Princeton, N.J.
Adler, Francis H., 313 S. 17th St., Philadelphia, Pa.
Aiken, S. D.,[1] 384 Post St., San Francisco 8, Calif.
Albaugh, C. H., 727 W. 7th St., Los Angeles 14, Calif.
Alberstadt, N. F., 921 Commerce Bldg., Erie, Pa.
Alexander, R. L., Euclid Ave. at 93rd St., Cleveland 6, Ohio.
Allen, James H.,[1-4] 1430 Tulane Ave., New Orleans 12, La.
Allen, Lee,[5] University Hosp. Iowa City, Ia.
Allen, Robert T.,[5] Indiana Univ. Med. Center, Indianapolis, Ind.
Allen, Thomas D., 2329 Pioneer Rd., Evanston, Ill.
Alvaro, Moacyr Eyck, 1151 Rua Consolacoa, São Paulo, Brazil
Alvis, Edmund B., 308 No. 6th St., St. Louis 1, Mo.
Anderson, Edwin R.,[5] 220 Liberty St., Warren, Pa.
Appelbaum, Alfred, 5905 Pacific Blvd., Huntington Park, Calif.
Armstrong, Richard C.,[1] 595 E. Colorado St., Pasadena 1, Calif.
Ascher, Charles K. W., 2914 Vernon Place, Cincinnati 19, Ohio
Atkinson, George S.,[5] 145 Elk Place, New Orleans 12, La.
Atkinson, Walter S., 129 Clinton St., Watertown, N.Y.
Auten, Hanford L., Hitchcock Clinic, Hanover, N.H.

B

Bahn, Charles A., 1026 Maison Blanche Bldg., New Orleans, La.
Bahn, Gustav C., 1028 Maison Blanche Bldg., New Orleans, La.
Baird, J. Mason, 511 Medical Arts Bldg., Atlanta, Ga.
Balding, Laurence G., 101 So. Madison, Pasadena 1, Calif.
Barkan, Hans, 2400 Clay St., San Francisco 15, Calif.
Barber, Aeleta N.,[1] Dept. Path., LSU Med. Sch., New Orleans, La.
Barkan, Otto, 490 Post St., San Francisco 2, Calif.
Barnett, Irving F., 30 N. Michigan Ave., Chicago 2, Ill.
Bassen, Edward J., 70 E. 66th St., New York, N.Y.
Beach, S. Judd,[2] 704 Congress St., Portland, Me.
Bedell, Arthur J., 344 State St., Albany, N.Y.
Beetham, Wm. P., 108 Bay State Rd., Boston, Mass.
Bell, Dudley P.,[1] 411—30th St., Oakland, Calif.
Bell, Richard P., Jr.,[5] University Hosp., Cleveland, Ohio.
Bellows, John G., 30 N. Michigan Blvd., Chicago 2, Ill.
Benedict, William L.,[1] Mayo Clinic, Rochester, Minn.
Benson, Clifton E.,[1] 245 Fourth St., Bremerton, Wash.
Berens, Conrad,[3] 35 E. 70th St., New York, N.Y.
Berry, A. Erwin, 1035 Grand Concourse, Bronx, N.Y.
Bettman, Jerome W.,[1] 2400 Clay St., San Francisco 15, Calif.

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[1] Attended 1950 Meeting
[2] Honorary Member
[3] Life Member
[4] Sustaining Member
[5] Educational Member

Billings, Robert J., Jenkins Arcade Bldg., Pittsburgh 22, Pa.
Bizzell, James W.,[5] Halloran VA Hosp., Staten Island, N.Y.
Blake, Eugene M., 303 Whitney Ave., New Haven 11, Conn.
Blazar, Howard A.,[5] Univ. of Pa. Hosp., Philadelphia, Pa.
Blodi, Frederick C., 635 W. 165th St., New York, N.Y.
Bloomenthal, Sanford R.,[5] Halloran VA Hosp., Staten Island, N.Y.
Blum, John, 44 Boulevard des Tranchees, Geneva, Switzerland.
Boles, William McDonald, 211 Loyola Ave., New Orleans 12, La.
Bonadia, Calogero,[5] Halloran VA Hosp., Staten Island, N.Y.
Borley, W. E.,[1] 655 Sutter St., San Francisco 2, Calif.
Boyd, James L., 10 Edge Hill Rd., Glen Cove, L.I., N.Y.
Boyes, Truman L., 654 Madison Ave., New York, N.Y.
Braley, Alson E., University Hosp., Iowa City, Ia.
Brandenburg, K. C., 110 Pine Ave., Long Beach 2, Calif.
Brandwan, Samuel R., 804 Rose Bldg., Cleveland, Ohio
Brault, Jules, 418 E. Sherbrooke St., Montreal, Quebec.
Brecher, Gerhard A.,[5] Dept. Physiology, Western Reserve Med. Sch., Cleveland, Ohio.
Bribach, E. J., 603 Commercial St., Atchison, Kan.
Bronk, Henry N., 708 Park Ave., New York 21, N.Y.
Brown, Albert L., 1137 Carew Tower, Cincinnati 2, Ohio.
Brown, E. V. L., 122 So. Michigan Ave., Chicago, Ill.
Browning, Charles W.,[3-5] Univ. Oregon Med. Sch., Portland, Ore.
Bruner, Abram B., 1214 Guardian Bldg., Cleveland, Ohio.
Bryan, James H., 3720 Washington Blvd., St. Louis 8, Mo.
Buesseler, John A.,[5] Dept. Ophth., Univ. of Pa. Hosp., Philadelphia, Pa.
Bulson, Eugene L., 347 W. Berry St., Fort Wayne 2, Ind.
Burch, Edward P., 424 Hamm Bldg., St. Paul, Minn.
Burdin, J. J.,[5] 105 Seville Blvd., Lafayette, La.
Burian, Hermann M., 520 Commonwealth Ave., Boston 15, Mass.
Burke, John W., 2000 Massachusetts Ave., N.W. Washington 6, D.C.
Burnett, Arthur B.,[5] Indiana Univ. Med. Center, Indianapolis, Ind.
Burr, Sherwood P., Jr.,[5] 43 E. Jackson St., Tucson, Ariz.
Butler, J. B. V., 909 Medical Dental Bldg., Portland, Ore.
Byrnes, Victor A., Sch. Aviation Med., Randolph Field, Tex.

C

Calhoun, F. Phinizy,[1] 478 Peachtree St., Atlanta 3, Ga.
Calkins, Larry L.,[5] Hospital Univ. Pa., Philadelphia 4, Pa.
Callahan, Alston, Dept Ophthal., Univ. Alabama Med. Sch., Birmingham, Ala.
Campion, George S.,[1] 490 Post St., San Francisco 2, Calif.
Carrasquillo, Honorio F., Med. Arts Bldg., Puerta de Tierra, Puerto Rico.
Carroll, Frank D., Blind Brook Lodge, Rye, N.Y.
Cary, Edward H., 631 Medical Arts Bldg., Dallas, Tex.
Casten, Virgil G., 412 Beacon St., Boston 15, Mass.
Castroviejo, Ramon, 9 E. 91st St., New York 28, N.Y.
Caylor, Robert N.,[5] Medical Arts Bldg., El Paso, Tex.
Chace, Robert R., 635 W. 165th St., New York 32, N.Y.
Chalfant, W. Paxson, Jr., 1915 16th St. N.W., Washington 9, D.C.
Chamberlain, Webb P., Jr., 7045 Detroit Ave., Cleveland 2, Ohio.
Chandler, Paul A., 5 Bay State Road, Boston 15, Mass.
Chickering, Donald H.,[5] 1842 Forest Hills Blvd., East Cleveland, Ohio.
Chisholm, Julian F., Jr., 34½ Beacon St., Boston, Mass.
Cholst, Mortimer,[5] 1 Nevins St., Brooklyn, N.Y.
Christensen, Leonard,[5] Univ. Oregon Med. Sch., Portland, Ore.
Clapp, Clyde A., 513 No. Charles St., Baltimore 1, Md.
Clark, Cecil P., 23 E. Ohio St., Indianapolis 4, Ind.
Clark, Charles E.,[5] 207 South Commerce, Natchez, Miss.
Clark, William B.,[1] 211 Loyola Ave., New Orleans 12, La.
Clothier, William L., 407 Kane Bldg., Pocatello, Idaho.
Cloutier, Roland, Medical Arts Bldg., Montreal 25, Quebec.
Cogan, David G., 243 Charles St., Boston, Mass.
Cohen, Martin, 29 E. 64th St., New York 21, N.Y.
Colson, Z. William, 301 Essex St., Lawrence, Mass.
Constantine, F. H., 30 W. 59th St., New York 19, N.Y.
Constantine, K. W., 229 Barton Ave., Palm Beach, Fla.
Cordes, Frederick C.,[1] 384 Post St., San Francisco 8, Calif.
Courtney, R. H., 401 Franklin St., Richmond, Va.
Covey, John K., 140 W. High St., Bellefonte, Pa.
Craig, Paul C., 232 No. 5th St., Reading, Pa.
Crawford, H. C., 705 Doctors Bldg., Atlanta 3, Ga.
Crawford, Joseph W.,[1] 490 Post St., San Francisco 2, Calif.
Crawford, Walter J., 3910 Market St., Riverside, Calif.
Crisp, William H., 1276 Emerson St., Denver, Colo.
Culler, Arthur M., 150 E. Broad St., Columbus, Ohio.
Cumming, Mrs. Edith L., Valley Cottage, N.Y.
Curtin, Brian J. H.,[5] 447 E. 14th St., New York 9, N.Y.
Cushman, Beulah, 25 E. Washington St., Chicago 2, Ill.
Cutler, Morton,[4] 1515 Addison Ave., E., Twin Falls, Idaho.

D

D'Amico, Thomas V.,[5] 70 Fairview Ave., Verona, N.J.
Dasilva, Antonio I., Rua Santa Catarina 1101, Belo Horizonte, Minas Gerais, Brazil, South America.
Day, R. M.,[5] Hospital, Univ. Pa., Philadelphia 4, Pa.
Dean, Alfred, 26 Sheldon Ave., Grand Rapids, Mich.
de Andrade, Cesario,[5] Bahia, Brazil.
DeLong, Samuel L., Univ. Hosp., 34th & Spruce Sts., Philadelphia 4, Pa.
Dennis, Richard H.,[5] 33 College Ave., Waterville, Me.
De Ocampo, Geminiano, Phil. Gen. Hosp., Manila, P.I.
DeVoe, Arthur G., 30 W. 59th St., New York 32, N.Y.
DeWitt, Edward N., 881 Lafayette St., Bridgeport 4, Conn.
Dickson, Owen C., 2628 Telegraph Ave., Berkeley, Calif.
Dillahunt, Jack A.,[5] Monroe at Copper, Albuquerque, N.M.
Dische, Zacharias,[1] 630 W. 168th St., New York, N.Y.
Downing, Arthur H., 406 Sixth Ave., Des Moines, Ia.
Duane, Thomas D., 87 W. Broad St., Bethlehem, Pa.
Duggan, John W.,[5] Wells Pavilion, Univ. Hosp., Edmonton, Alberta.
Duke-Elder, Lady Phyllis,[2] London, England.
Duke-Elder, Sir Stewart,[2] London, England.
Dunnaven, Floyd L., 514 Medical Arts Bldg., Vancouver, Wash.
Dunnington, John H.,[4] 635 W. 165th St., New York 32, N.Y.
Durham, Davis G., Medical Arts Bldg., Wilmington, Del.
Dyar, Edwin W.,[1] 3202 No. Meridian St., Indianapolis 8, Ind.
Dyson, Charles, 283 Queens Ave., London, Ontario.

E

Ehrenfeld, Edward, 185 Lexington Ave., Passaic, N.J.
Elles, Norma B., 800 Travis St., Houston 2, Tex.
Elliot, Alfred J., 170 St. George St., Toronto 5, Ontario.
Ellis, Orwyn H.,[1] 523 W. 6th St., Los Angeles 14, Calif.
Elvin, Norman L., 309 Med. Arts Bldg., Winnipeg, Manitoba.
Emerson, George O.,[5] N.Y. Eye & Ear Infirm., New York 3, N.Y.
Engel, Samuel,[1] 350 Post St., San Francisco 8, Calif.
Ernst, Marie K.,[5] 1411 So. Albany Ave., Tampa 6, Fla.
Evans, John N., 23 Schermerhorn St., Brooklyn 2, N.Y.
Evans, Samuel D., 1502 Park Bldg., Pittsburgh 22, Pa.
Evans, William H., 510 Dollar Bank Bldg., Youngstown, Ohio.

F

Falls, Harold F.,[1] Univ. Hosp., Ann Arbor, Mich.
Ferrer, Horatio,[2] Havana, Cuba.
Fine, Max,[1] 655 Sutter St., San Francisco 2, Calif.
Fink, Austin I., 110 Remsen St., Brooklyn 2, N.Y.
Fink, Walter H.,[1] 1029 Medical Arts Bldg., Minneapolis 2, Minn.
Finkelstein, Julius,[5] 1320 Foucher St., New Orleans, La.
Fisher, James A.,[5] Med. Arts Bldg., 601 Grand Ave., Asbury Park, N.J.
Fixott, R. S., 624 Medical Arts Bldg., Portland, Ore.
Flanagan, Roger M.,[5] Univ. Oregon Med. Sch., Portland, Ore.
Flick, John J., 1443 No. Pennsylvania, Indianapolis, Ind.
Flynn, John E.,[5] 526 East 20th St., New York 9, N.Y.
Fonda, G. E.,[4] 6 Parkview Drive, Millburn, N.J.
Foote, Franklin M.,[1] 1790 Broadway, New York, N.Y.

Fralick, F. Bruce, 408 1st Natl. Bank Bldg., Ann Arbor, Mich.
Franks, Myron B.,[5] 401 Hotel Jamestown Bldg., Jamestown, N.Y.
Freeman, Sheldon B., 196 Linwood Ave., Buffalo, N.Y.
Friedell, H. L., 2065 Adelbert Road, Cleveland, Ohio.
Friedenwald, Jonas S., 1212 Eutaw Place, Baltimore 17, Md.
Friedman, Benjamin, 160 W. 73rd St., New York 24, N.Y.
Frink, Berton F.,[5] Dept. Ophthal., N.Y. Univ., New York, N.Y.
Fritschi, Ulrich A., 523 Medico Dental Bldg., Sacramento 14, Calif.

G

Gallardo, Edward, 153 Marquette St., LaSalle, Ill.
Gans, Jerome A., 922 Keith Bldg., Cleveland 15, Ohio.
Gans, Morris E., 1621 Euclid Ave., Cleveland 15, Ohio.
Garron, Levon K., 426 17th St., Oakland 12, Calif.
Gehrsitz, Leta B.,[1-5] 5310 No. Williams Ave., Portland 11, Ore.
Gifford, Harold, 1620 Med. Arts Bldg., Omaha, Neb.
Gilbert, Ralph H., 110 Fulton St., E., Grand Rapids 2, Mich.
Gilger, Anita P., 2571 W. 7th St., Cleveland 15, Ohio.
Gill, Earl K., 806 Medical-Professional Bldg., Corpus Christi, Tex.
Gill, Wm. D., Medical Arts Bldg., San Antonio 5, Tex.
Gillette, David F., 109 Warren St., Syracuse, N.Y.
Ginsberg, Joseph,[5] Mass. Eye & Ear Infirm., 243 Charles St., Boston 14, Mass.
Givner, Isadore, 108 E. 66th St., New York 16, N.Y.
Goar, Everett L., 1304 Walker Ave., Houston 2, Tex.
Goldberg, Sol, 8082 Jenkins Arcade, Pittsburgh 22, Pa.
Goodfellow, Thomas J., 20 Arcade Bldg., Saratoga Springs, N.Y.
Graham, John H., 4275 Pearl Rd., Cleveland 9, Ohio.
Grand, Hendrie W., 330 Lowry Med. Arts Bldg., St. Paul, Minn.
Grant, V. Morton, 243 Charles St., Boston 14, Mass.
Gray, John E.,[1] 2615 Capitol Ave., Sacramento 16, Calif.
Gresser, Edward B., 39 E. 75th St., New York 21, N.Y.
Guibor, George P., 30 No. Michigan Ave., Chicago 2, Ill.
Gundersen, Trygve, 101 Bay State Rd., Boston 15, Mass.
Guy, Loren P., 40 E. 62nd St., New York 21, N.Y.
Guyton, Jack S., Johns Hopkins Hosp., Baltimore 5, Md.

H

Haessler, F. Herbert, 545 No. 15th St., Milwaukee 3, Wis.
Hallett, Joseph W., Medical Arts Bldg., Philadelphia, Pa.
Haney, Lawrence O.,[5] 145 Elk Place, New Orleans, La.
Harbridge, Delamere, 12 No. Central Ave., Phoenix, Ariz.
Hardesty, Hiram H., 10515 Carnegie Ave., Cleveland 6, Ohio.
Hardesty, John F., 634 No. Grand Blvd., St. Louis, Mo.
Hardy, LeGrand H., 23 E. 79th St., New York, N.Y.
Hare, James,[5] Crile VA Hosp., Cleveland, Ohio.
Hare, Robert, 416 No. Bedford Drive, Beverly Hills, Calif.
Harger, Robert W.,[5] 1040 W. Michigan St., Indianapolis 7, Ind.
Harley, Halvor L., 101 S. Indiana Ave., Atlantic City, N.J.
Harley, Robison D., 101 S. Indiana Ave., Atlantic City, N.J.
Harrington, David O.,[1] 384 Post St., San Francisco 8, Calif.
Harris, John E.,[1-5] Walter Reed Gen. Hosp., Washington, D.C.
Hartenbower, G. E.,[4] 410 Unity Bldg., Bloomington, Ill.
Hartman, Deane C., 727 W. 7th St., Los Angeles 14, Calif.
Hartshorne, Isaac, 30 W. 59th St., New York 19, N.Y.
Harvey, Elmer F., 942 Hanna Bldg., Cleveland 15, Ohio.
Hawks, Gordon H.,[5] Banting Inst., 100 College St., Toronto, Ontario.
Heare, Louis C.,[1] 221 Bluestein Bldg., Port Arthur, Tex.
Heath, Parker, 243 Charles St., Boston 14, Mass.
Heitger, Jos. D., 701 Heyburn Bldg., Louisville, Ky.
Henderson, John W., 102 Second Ave. S.W., Rochester, Minn.
Henderson, John W., Univ. Hosp., Ann Arbor, Mich.
Henderson, Lawrence E., 139 Clinton St., Watertown, N.Y.
Henry, Alvin L.,[5] Indianapolis Gen. Hosp., Indianapolis, Ind.
Henry, Margaret,[1] 384 Post St., San Francisco 8, Calif.
Hester, Marion W., 1255 Lakeland Hills Blvd., Lakeland, Fla.
Hildreth, H. Rommel,[1] 3720 Washington Blvd., St. Louis 8, Mo.
Hilgartner, H. L., 202 W. 13th St., Austin, Tex.
Hill, Howard F., Professional Bldg., Waterville, Me.
Hill, John M.,[5] N.Y. Eye and Ear Infirm., New York, N.Y.
Hill, Robert V.,[5] Univ. of Oregon Med. Sch., Portland, Ore.
Hogan, Michael J.,[1] 450 Sutter St., San Francisco, Calif.
Holmes, Dorothy B., 1816 R St. N.W., Washington 9, D.C.
Holmes, William J.,[1] 45 Alexander Young Bldg., Honolulu 9, T.H.
Holstein, Theodore, 411 Medico-Dental Bldg., Sacramento 14, Calif.
Holzer, Wm. F., 36 Pleasant St., Worcester 8, Mass.
Howard, Harvey J., Park Plaza Hotel, St. Louis, Mo.
Howell, Homer P.,[1] 3022 E. 14th St., Oakland 1, Calif.
Hughes, Wm. F., Hume Mansur Bldg., Indianapolis 4, Ind.
Hughes, Wm. F., Jr.,[1] 536 Sheridan Rd., Evanston, Ill.

I

Imus, Henry A.,[1] 907 Crescent Dr., Alexandria, Va.
Ingalls, Raymond G., 635 W. 165th St., New York 32, N.Y.
Irvine, A. Ray, 727 W. 7th St., Los Angeles 14, Calif.
Irvine, Rodman,[1] 727 W. 7th St., Los Angeles, Calif.
Irvine, Wendell C., 727 W. 7th St., Los Angeles, Calif.

J

Jacobson, Jerry H.,[5] N.Y. Eye & Ear Infirm., New York, N.Y.
Jacoby, M. W., 1364 Hanna Bldg., Cleveland 15, Ohio.
Jakobovits, Rafael, 655 Sutter St., San Francisco 2, Calif.
James, Wm. M., 3720 Washington Blvd., St. Louis 8, Mo.
Jensen, Carl D. F., Medical-Dental Bldg., Seattle 1, Wash.
Johns, Juanita P., 313 Commonwealth Ave., Boston, Mass.
Johnson, Hobart Clemens, 839 Belgrade Ave., Mankato, Minn.
Johnson, Lorand V.,[1-4] 10515 Carnegie Ave., Cleveland 8, Ohio.
Johnson, Samuel B.,[5] 145 Elk Place, New Orleans 12, La.
Judd, John Hewitt, 1020 Med. Arts Bldg., Omaha, Neb.

K

Kadin, Maurice, 535 Main St., Racine, Wis.
Kahan, Edmund,[5] 200 W. 93rd St., New York, N.Y.
Kahler, Arthur R., 2615 Capitol Ave., Sacramento 16, Calif.
Katz, Dewey, 99 Pratt St., Hartford 3, Conn.
Key, Samuel N., Jr.,[4] 120 W. 7th St., Austin, Tex.
Keyes, John E. L., 22199 McCauley Rd., Cleveland 22, Ohio.
Kilgore, George L., 411 Thorn St., San Diego 3, Calif.
King, George L., 537 E. Market St., Alliance, Ohio.
King, John H., Jr., Tripler General Hosp., Honolulu, T.H.
Kinsey, V. E., Kresge Eye Institute, Detroit, Mich.
Kirby, Daniel B., 780 Park Ave., New York 21, N.Y.
Kirk, Robert C.,[5] 3399 Warren Rd., Cleveland, Ohio.
Kirkland, Theo N., Jr.,[5] 1711 Milan St., New Orleans, La.
Knapp, Arnold, 10 E. 54th St., New York 22, N.Y.
Knapp, Arthur A., 112 E. 73rd St., New York, N.Y.
Knighton, Willis S., 121 E. 61st St., New York, N.Y.
Knowles, F. Edwin, Jr., 513 N. Charles St., Baltimore 1, Md.
Koch, F. L. P., 60 E. 75th St., New York, N.Y.
Koenig, Ivan J.,[5] 40 N. St., Buffalo 2, N.Y.
Kornzweig, Abraham L., 1200 Fifth Ave., New York, N.Y.
Kottler, Saul, 831 Guardian Bldg., Cleveland 14, Ohio.
Krause, Arlington C., 950 E. 59th St., Chicago, Ill.
Krewson, Wm. E. III, 1930 Chestnut St., Philadelphia, Pa.
Kronfeld, Peter C., 109 N. Wabash Ave., Chicago 2, Ill.
Krug, Joseph H., 988 Fifth Ave., New York 21, N.Y.

Kuhn, Hedwig S., 60 Glendale Park, Hammond, Ind.

L

Laird, Robert G., Metz Bldg., Grand Rapids 2, Mich.
Lancaster, Walter B.,[2] 520 Commonwealth Ave., Boston 15, Mass.
Larkin, Bernard J., 305 Hume-Mansur Bldg., Indianapolis 4, Ind.
Last, Murray A.,[4] 1095 Park Ave., New York, N.Y.
Laval, Joseph, 136 E. 64th St., New York, N.Y.
Leckert, Edmund L., Jr.,[6] 211 Loyola Ave., New Orleans 12, La.
Lee, Otis S., Springer Clinic, Tulsa, Okla.
Leinfelder, P. J., Univ. Hosp., Iowa City, Ia.
Lemoine, A. N.,[1] 411 Alameda Rd., Country Club Plaza, Kansas City 2, Mo.
Lemoine, A. N., Jr., 411 Alameda Rd., Country Club Plaza, Kansas City 2, Mo.
Leopold, Irving H., 1930 Chestnut St., Philadelphia 3, Pa.
Lepard, C. W., 1025 David Whitney Bldg., Detroit 26, Mich.
Lerner, Macy L., 332 Park Ave., Rochester 7, N.Y.
Levy, Abram, 1401 Plainfield Ave., South Plainfield, N.J.
LeWin, Thurber,[1-6] 112 Linwood Ave., Buffalo, N.Y.
Lewis, Philip M., Exchange Bldg., Memphis 3, Tenn.
Liebman, Sumner D., 115 Bay State Rd., Boston 15, Mass.
Linn, Jay G. Jr., 7075 Jenkins Arcade Bldg., Pittsburgh 22, Pa.
Linn, Jay G. Sr., 7075 Jenkins Arcade Bldg., Pittsburgh 22, Pa.
Lipp, Frank E., City Natl. Bank Bldg., Omaha 2, Neb.
Little, Milton F., 49 Pearl St., Hartford, Conn.
Lloyd, Ralph I., 14 8th Ave., Brooklyn 17, N.Y.
Locke, John C.,[5] 635 W. 16th St., New York 32, N.Y.
Lordan, John P.,[5] 9730 Wilshire Blvd., Beverly Hills, Calif.
Loutfallah, Michael,[1] 1826 State St., Santa Barbara, Calif.
Luedde, Philip S., 311 Metropolitan Blvd., St. Louis 3, Mo.
Luedde, William H., 508 No. Grand Ave., Buffalo, N.Y.
Luhr, John P.,[5] 625 Linwood Ave., Buffalo, N.Y.
Lutman, Frank C., Germantown Professional Bldg., Philadelphia 44, Pa.
Lyle, Donald J., 601 Union Trust Bldg., Cincinnati 2, Ohio.

Mc

McAlester, A. W., III, 2003 Bryant Bldg., Kansas City, Mo.
McAlpine, Paul T., 129 Summit Ave., Summit, N.J.
McBain, Earle, H.,[1] 490 Post St., San Francisco 2, Calif.
McCallum, George C., 301 Eugene Med. Center, Eugene, Ore.
McCannel, Malcolm A., 1918 Med. Arts Bldg., Minneapolis 2, Minn.
McCulloch, Clement, 830 Med. Arts Bldg., Toronto, Ontario.
McDonald, Philip R.,[1] 1930 Chestnut St., Philadelphia 3, Pa.
McGarvey, William E., 802 Jackson City Bank Bldg., Jackson, Mich.
McGavic, John S., 601 Montgomery Ave., Bryn Mawr, Pa.
McGuire, William P., 105 N. Braddock St., Winchester, Va.
McKay, Edward D., Scott and White Clinic, Temple, Tex.
McKee, Joseph W., 1105 Grand Ave., Kansas City 6, Mo.
McLean, John M., 525 E. 68th St., New York 21, N.Y.
McRae, John H., Med. Arts Bldg., Grand Rapids 2, Mich.

M

MacDonald, Alexander, 10 Edgar Ave., Toronto, Ontario.
MacDonald, Roy K.,[6] 15 Walmsley Blvd., Toronto, Ontario.
MacLean, Angus L., 1201 N. Calvert St., Baltimore 2, Md.
Madeley, H. Randall, 727 Sonoma St., Vallejo, Calif.
Magee, George R., 1331 Hillside Dr., Reno, Nev.
Makley, Torrence A.,[5] Univ. Hosp., Columbus, Ohio.
Mandelbaum, Joseph, 101 Lafayette Ave., Brooklyn 17, N.Y.
Mann, William A., 30 N. Michigan Ave., Chicago 2, Ill.
Mannis, Aaron A., 109 N. Wabash Ave., Chicago, Ill.
Marshall, M. R.,[4] Wells Pavilion, Univ. Hosp., Edmonton, Alberta.
Martz, George E., 505 No. 2nd St., Harrisburg, Pa.
Masters, Robert J., 805 Hume-Mansur Bldg., Indianapolis 4, Ind.
Matthews, John L.,[4] 929 Nix Professional Bldg., San Antonio 5, Tex.
Maumenee, Alfred E.,[1] Stanford Univ. Hosp., San Francisco 15, Calif.
Meisenbach, Albert E., Jr., 300 Med. Arts Bldg., Dallas 9, Tex.
Merriam, George R., Jr., 635 W. 165th St., New York 32, N.Y.
Mesirow, M. E.,[4] 117 E. Cook, Santa Maria, Calif.
Meyer, George P., 410 Haddon Ave., Camden, N.J.
Meyer, Samuel J., 109 N. Wabash, Chicago 2, Ill.
Miles Paul W.,[1] 640 S. Kingshighway, St. Louis 10, Mo.
Miller, Claude K., 30 S. Wenatchee St., Wenatchee, Wash.
Miller, George L., 14805 Detroit Ave., Lakewood, Ohio.
Milller, Miriam,[1] 350 Post St., San Francisco 8, Calif.
Mills, Dawson A.,[5] US Naval Hosp., Newport, R.I.
Mills, Lloyd, 609 S. Grand Ave., Los Angeles, Calif.
Mims, James L., Jr.,[5] Medical Arts Bldg., San Antonio, Calif.
Minsky, Henry, 2 E. 95th St., New York, N.Y.
Moore, Paul G., 1701 Republic Bldg., Cleveland, Ohio.
Morgan, James C., Jr.,[5] 145 Elks Place, New Orleans, La.
Morgan, Meredith W., Jr.,[1] 911 MacDonald Ave., Richmond, Calif.
Morris, Jean W.,[5] Johnston Bldg., Muncie, Ind.
Morrison, W. Howard, 1500 Med. Arts Bldg., Omaha 2, Neb.
Mortensen, Andreas V. M.,[5] 458 Government St., Mobile 12, Ala.
Motto, M. Paul, 650 Rose Bldg., Cleveland, Ohio.
Mullen, Carroll R., 2025 Locust St., Philadelphia 3, Pa.
Myers, Roscie W., 36 Pleasant St., Worcester 8, Mass.

N

Nadbath, Rudolph P.,[5] U. S. Naval Hosp., Portsmouth, Va.
Nelson, Robert C.,[5] 14058 Superior Rd., Cleveland Heights 18, Ohio.
Nethercut, Glenway W., 25 E. Washington St., Chicago 2, Ill.
Newell, Frank W., 30 N. Michigan Ave., Chicago 2, Ill.
Nicholl, Russell J., 10515 Carnegie Ave., Cleveland 6, Ohio.
Noble, Bertha R.,[6] 211 Loyola Ave., New Orleans 12, La.
Norene, Robert A., 727 W. 7th St., Los Angeles 14, Calif.
Norton, Herman J., Jr.,[5] 409 University Pk., Rochester, N.Y.
Nosik, William A., 10515 Carnegie Ave., Cleveland 6, Ohio.
Novak, Joseph F., 807 Empire Bldg., Pittsburgh 22, Pa.
Nugent, Maurice W., 2007 Wilshire Blvd., Los Angeles 5, Calif.

O

Oakley, Kenneth H., 129 N. Jackson St., Roseburg, Ore.
Oaks, Lewis, W.,[1] 677 N. University Ave., Provo, Utah.
O'Brien, Cecil S., 43 E. Jackson St., Tucson, Ariz.
Odom, Robert E., 510 Dollar Bank Bldg., Youngstown, Ohio.
Ogle, Kenneth N.,[1] Mayo Clinic, Rochester, Minn.
Ohly, John H.,[4] 22 Schermerhorn St., Brooklyn 2, N.Y.
Orbison, James L.,[5] Inst. Path., Western Reserve Univ., Cleveland 6, Ohio.
Ormsby, Hugh L., 75 Sutherland Dr., Leaside, Toronto 17, Ontario.
O'Rourke, Donald H., 920 Republic Bldg., Denver 2, Colo.
Osler, Jay K., 5 Grove St., Bangor, Me.
Owens, William C., Johns Hopkins Hosp., Baltimore 5, Md.
Ozment, Thomas L.,[5] Eye & Ear Hosp., Pittsburgh 13, Pa.

P

Pang, Herbert G.,[5] Manhattan Eye & Ear Hosp., 210 E. 64th St., New York 21, N.Y.
Parker, Walter R.,[3] 1551 Woodward Ave., Detroit, Mich.
Paton, Leslie,[3] London, England.
Paton, R. Townley, 927 Park Ave., New York, N.Y.

Paul, Thomas O., 2205 Highland Ave., Birmingham 5, Ala.
Payne, Brittain F.,[4] 17 E. 72nd St., New York, N.Y.
Perera, Charles A., 70 E. 66th St., New York, N.Y.
Pettit, William A., 727 W. 7th St., Los Angeles, Calif.
Pfingst, Harry A.,[3] 1015 Heyburn Bldg., Louisville 2, Ky.
Phillips, Josephine D., 2010 E. 102nd St., Cleveland 6, Ohio.
Pichette, Henri, 425 St. John St., Quebec City, Quebec.
Pinkoson, Charles,[8] Charity Hosp., New Orleans, La.
Pischel, Dohrmann K., 490 Post St., San Francisco 2, Calif.
Plumer, John S., 121 University Place, Pittsburgh 13, Pa.
Post, Lawrence T., 508 N. Grand Blvd., St. Louis 3, Mo.
Post, Martin H., Jr., 520 Metropolitan Bldg., St. Louis, Mo.
Potter, Wm. Bentley, 521 22nd St., Galveston, Tex.
Potts, Albert M.,[6] Dept. Surg., Western Reserve Univ., Cleveland 6, Ohio.
Prangen, Avery D., Mayo Clinic, Rochester, Minn.

R

Radewan, Milton G., 30 S. Wenatchee Ave., Wenatchee, Wash.
Raffo, Julio C., Gremios #465, Lima, Peru, S. A.
Ralph, Fenn T.,[8] 193 Clinton Ave., Brooklyn, N.Y.
Rasgorshek, Robert H.,[1] 425 Aquila Court, Omaha, Neb.
Ravdin, Emile M., 4036 Wilshire Blvd., Los Angeles 5, Calif.
Reeder, James E., Jr., 523 Davidson Bldg., Sioux City 13, Ia.
Reeh, Merrill J., 919 S.W. Taylor St. Bldg., Portland 5, Ore.
Reese, Algernon B.,[4] 73 E. 71st St., New York 21, N.Y.
Reese, Warren S., 2118 Locust St., Philadelphia 3, Pa.
Regan, James J., 520 Commonwealth Ave., Boston 15, Mass.
Reid, Frederick K., 500 N. George St., Rome, N.Y.
Reid, Horace W., 2205 Union Central Bldg., Cincinnati 2, Ohio.
Reid, John J., Jr., 105 E. 63rd St., New York 21, N.Y.
Reitz, Herbert R., 446 Linwood Ave., Buffalo, N.Y.
Riddle, Ransford J., 14 Porter Way, Sharon, Pa.
Rigg, James P., 52 Rood Ave., Grand Junction, Colo.
Robbins, Alfred R., 1930 Wilshire Blvd., Los Angeles 5, Calif.
Roberts, Walter L., 8225 Ramsgate, Los Angeles, Calif.
Rodin, Frank H.,[3] 490 Post St., San Francisco 2, Calif.
de Roetth, Andrew F. M.,[4] 1006 Overbluff, Spokane, Wash.
de Roetth, Andrew, Jr.,[1-8] 635 W. 165th St., New York 32, N.Y.
Romaine, Hunter, 111 E. 65th St., New York 21, N.Y.
Romejko, Walter J., 1810 K St., N.W., Washington 6, D.C.
Roper, Kenneth L., 58 E. Washington St., Chicago 2, Ill.
Rosenbaum, Harry D., 3720 Washington Blvd., St. Louis, Mo.
Rosenberg, Abner S., 142 Joralemon St., Brooklyn 2, N.Y.
Rosenthal, Benjamin C., 140 New York Ave., Brooklyn 16, N.Y.
Rosner, Robert S., 10300 Carnegie Ave., Cleveland 6, Ohio.
Ross, Cecilia, 1318 Second St., Santa Monica, Calif.
Ross, Joseph V. M., 321 E. Front St., Berwick, Pa.
Rowland, Louise S., Wilmer Inst. Johns Hopkins Hosp., Baltimore, Md.
Rowland, William M., 1118 St. Paul St., Baltimore, Md.
Rucker, C. Wilbur,[1] Mayo Clinic, Rochester, Minn.
Ruedemann, A. D.,[4] 1633 David Whitney Bldg., Detroit 26, Mich.
Rutherford, Cyrus W.,[3] 4601 No. Pennsylvania St., Indianapolis, Ind.
Rychener, Ralph O., 130 Madison Ave., Memphis 3, Tenn.

S

Sakler, Barnet R., 19 Garfield Place, Cincinnati 2, Ohio.
Saltzman, Samuel L., 334 W. 86th St., New York 25, N.Y.
Samuels, Bernard, 57 W. 57th St., New York, N.Y.
Sanders, T. E., 3720 Washington Blvd., St. Louis 8, Mo.
Sanders, N. P., 901 20th St. N.W., Washington 6, D.C.
Sauer, John J., 30 E. 40th St., New York, N.Y.
Schachat, Walter S. 30 E. 60th St., New York 22, N.Y.
Scheie, Harold G.,[1] 313 S. 17th St., Philadelphia 3, Pa.
Schepens, Charles L., 243 Charles St., Boston, Mass.
Schmerl, Ernst, Inst., Med. Research, 2805 Oatis Ave., Toledo 6, Ohio.
Shoch, David E.,[8] Northwestern U. Med. Sch., Chicago, Ill.
Schoel, Robert E.,[8] 211 Loyola Ave., New Orleans, La.
Scholz, Roy O., 11 E. Chase St., Baltimore 2, Md.
Schonberg, Albert L., 414 N. Adams, Albuquerque, N.Mex.
Schultz, Jacob F., 1304 Walker Ave., Houston 5, Tex.
Schuster, Stephen A., First Natl. Bank Bldg., El Paso, Tex.
Schwartz, Frank E.,[8] Walter Reed Gen. Hosp., Washington, D.C.
Schwartz, Frederick O., 508 N. Grand Blvd., St. Louis 3, Mo.
Schwarz, Gerald T., 10515 Carnegie Ave., Cleveland 6, Ohio.
Scobee, Richard G., 640 S. Kingshighway, St. Louis 10, Mo.
Shaffer, Robert N., 490 Post St., San Francisco, Calif.
Shahan, Philip T., 508 N. Grand Ave., St. Louis 3, Mo.
Shahan, William E., 508 N. Grand Blvd., St. Louis 3, Mo.
Shapira, Theodore M., 109 N. Wabash Ave., Chicago 2, Ill.
Shapiro, Ernest K.,[8] 20-57 18th St. Long Island City 5, N.Y.
Sharbaugh, George B., 212 W. State St., Trenton 8, N.J.
Sheard, Charles, Mayo Clinic, Rochester, Minn.
Sheppard, L. Benjamin, 301 Med. Arts Bldg., Richmond 19, Va.
Sherman, A. Russell, 671 Broad St., Newark, N.J.
Sherman, Elbert S., 671 Broad St., Newark, N.J.
Shusterman, Morris, Banting Inst., Toronto, Ontario.
Siegel, Edward, 45 Oak St., Plattsburg, N.Y.
Sitchevaska, Olga, 30 Fifth Ave., New York 11, N.Y.
Sitney, J. J., 6363 Wilshire Blvd., Los Angeles 48, Calif.
Sloan, Henry L., 106 W. 7th St., Charlotte 2, N.C.
Smith, E. Gerard, 339 N. Duke St., Lancaster, Pa.
Smith, E. Terry,[4] P.O. Box 43, West Hartford, Conn.
Smith, Homer E., 54 E. South Temple St., Salt Lake City 1, Utah.
Smith, Jaroud B., Jr., U. S. Naval Hosp., Chelsea, Mass.
Smith, James W., 1016 Fifth Ave., New York 28, N.Y.
Smith, John T., BuMed, Navy Dept., Washington 25, D.C.
Smith, Joseph G., 490 Post St., San Francisco, Calif.
Smithson, Robert A., Jr.,[1-8] 6616 Aseat Drive, Oakland 11, Calif.
Snell, Albert C., 53 S. Fitzhugh St., Rochester, N.Y.
Snyder, M. Wilson, 14 Porter Way, Sharon, Pa.
Sommers, Ignatius G.,[3] 981 S. Westmoreland Ave., Los Angeles 6, Calif.
Spaeth, Edmund B., 1930 Chestnut St., Philadelphia 3, Pa.
Steinberg, Bernhard, Inst. Med Research, 2805 Oatis Ave., Toledo 6, Ohio.
Steinberg, Theodore, 603 Patterson Bldg., Fresno, Calif.
Stevens, Ralph W., Baker Bldg., Walla Walla, Wash.
Stillerman, Manuel L., 109 N. Wabash Ave., Chicago 2, Ill.
Stine, George H., 304 Burns Bldg., Colorado Springs, Colo.
Stine, George T., 327 E. State St., Columbus 16, Ohio.
Stoddard, Kenneth B., 302 LeConte Hall, Univ. Calif., Berkeley, Calif.
Stolzar, Irwin H., 831 Guardian Bldg., Cleveland, Ohio.
Stone, William J., 1101 Beacon St., Brookline, Mass.
Sugar, H. Saul, 311 Kales Bldg., Detroit 26, Mich.
Suie, Ted,[8] Dept. Bacteriology, Ohio State, Columbus, Ohio.
Sullivan, Charles T., 277 Alexander St., Rochester, N.Y.
Sullivan, John V.,[8] 207 United Bldg., Akron 8, Ohio.
Swab, Charles M., 1316 Medical Arts Bldg., Omaha, Neb.
Swan, Kenneth C.,[1] 3181 S.W. Marquam Hill Rd., Portland 1, Ore.
Sykowski, Peter S.,[1] 1330 Union St., Schenectady 8, N.Y.

T

Tait, Edwin Forbes, 1324 W. Main St., Norristown, Pa.

Talbot, Thomas Edward,[5] Univ. of Oregon Med. Sch., Portland, Ore.
Tanner, Owen R.,[1] 300 Homer Ave., Palo Alto, Calif.
Tassman, Isaac S., 711 Med. Arts Bldg., Philadelphia, Pa.
Taylor, E. Merle, 1020 S.W. Taylor, Portland, Ore.
Theobald, G. D., 715 Lake St., Oak Park, Ill.
Theodore, Frederick H., 667 Madison Ave., New York 21, N.Y.
Thigpen, Charles A., 401 S. Court St., Montgomery 5, Ala.
Thomas, Charles I., 10505 Carnegie Ave., Cleveland 6, Ohio
Thomas, Harry V.,[4] Empire Bank Bldg., Clarksburg, W.Va.
Thomas, John Howard, 262 E. Market St., Warren, Ohio.
Thomas, Maxwell, 206 Med. Arts Bldg., Dallas, Tex.
Thompson, Edward H., 19 W. 7th St., Cincinnati, Ohio
Thorpe, Harvey E.,[4] 323 Jenkins Arcade, Pittsburgh 22, Pa.
Thygeson, Phillips,[1–4] 87 N. 6th St., San Jose, Calif.
Tinkess, Donald E., Ituri Towers, Greenwich, Conn.
Tracht, Robert R., 404 Lowry Med Arts Bldg., St. Paul 2, Minn.
Troncoso, Manuel U., 217 S. Ocean Ave., Freeport, L.I., N.Y.
Trowbridge, Dwight Howe, Jr., 2900 Fresno St., Fresno, Calif.
Trueman, Robert H., 600 N. 16th St., Philadelphia 30, Pa.
Truhlsen, Stanley M.,[5] 600 S. Kingshighway, St. Louis 10, Mo.
Tusak, Ervin A., 115 E. 90th St., New York 28, N.Y.
Tyner, George S.,[5] Univ. of Pa. Hosp., Philadelphia, Pa.

V

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von Sallmann, Ludwig,[1] 635 W. 165th St., New York 32, N.Y.

W

Waldman, Joseph, 1930 Chestnut St., Philadelphia 3, Pa.
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